Medicaid Dossier for *Treximet*

This information is provided in response to your request for information about *Treximet*™ (sumatriptan and naproxen sodium) Tablets. *Treximet* is a single-tablet formulation of sumatriptan 85 mg, formulated with RT Technology™, and naproxen sodium 500 mg.

Some information contained in this response may not be included in the approved Prescribing Information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

This Dossier is provided as a professional service in response to your unsolicited request. Confidential information may be provided within this Dossier. GSK requests that the recipient of this Dossier only share the contents with the Pharmacy & Therapeutics (P&T) Committee members for the purposes of making evidence-based decisions regarding formulary inclusion.

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1. EXECUTIVE SUMMARY

Migraine is a Multimechanistic Disease

Current understanding of the pathophysiology of migraine suggests that there are multiple mechanisms involved, including neurochemical release, vasodilation, inflammation, and prostaglandin production.[1,2,3] Individual migraine-specific monotherapies address some, but not all of the multiple components of migraine.

Acute Migraine Therapy: Stratified Care Proven Superior to Step Care

Available guidelines recommend various treatment options treatment of acute migraine. Results of the Disability in Strategies of Care (DISC) Study showed that stratified care provided a significantly greater response and less disability time across 6 attacks compared with step care across attacks and step care within attacks. [4]

Opportunities for Improvement:

Patients are Currently Selecting Step Care Approach to Managing Migraine

Data suggest that patients with access to multiple acute migraine therapies are practicing step care. A survey of 425 migraineurs showed that 71% used multiple medications to treat their migraines.[5] Over half reported using a step care approach within attack, and 17% used a rescue medication. Similarly, in a managed care population of migraineurs who had previously treated an attack with a triptan plus an NSAID, approximately one quarter chose to treat their next attack with an NSAID first, followed by a triptan later.[6]

Use of Opioids/Narcotics is Prevalent

Data also show that the use of opioids and narcotics is extensive. An analysis of migraineurs in a large managed care database found that 38% of migraine patients compared to 24% for matched controls had filled a narcotic.[7] Alarmingly, 7% of migraine cases filled only narcotic medications with no fills for other medications commonly used to treat headache.

Current Therapies Don't Always Work and Result in Redosing or Use of Rescue

Baseline demographics from two studies evaluating patients refractory to short-acting triptans showed that the most common reason for study enrollment was lack of efficacy with prior therapy.[8,9]

Dissatisfaction with Current Therapy

At screening for a long-term safety study, only about half of patients considered themselves to be satisfied or very satisfied with their previous treatment.[10] Not surprisingly, a study by Bigal, et al showed that 80% of patients would be willing to try another acute migraine therapy.[11]

Treximet: Distinct Pharmacokinetic Profile

Treximet is a single tablet containing 85 mg sumatriptan, as the succinate salt, formulated with RT Technology™ and 500 mg naproxen sodium. *Treximet* is formulated with a distinct pharmacokinetic profile that aligns with and targets the multiple mechanisms of migraine.[12] [13]

TREXIMET: extensive Clinical Trial Program

Over 3,500 patients have treated approximately 30,000 migraine attacks to date with *Treximet*.[14]

The clinical program for *Treximet* is comprised of ten randomized, double-blind, placebo-controlled, multicenter studies.[15,16] [8,9,17,18] [19,20,21,22] In addition, a 12-month, open-label, multi-attack, repeat-dose study was completed.[23]

Treximet: Superior Efficacy Versus Sumatriptan 85 mg

Treximet provided superior results across a variety of efficacy outcomes versus sumatriptan 85 mg in two randomized, double-blind trials in patients treating moderate-to-severe migraine pain.[15,16,24]

Treximet: Efficacy at Early Timepoints

Treximet provided superior pain relief and pain free results at 2 and 4 hours across multiple studies evaluating treatment of moderate-to-severe migraine pain or mild migraine pain.[15,16] [8,9,17,18,19,20] *Treximet* also provided superior migraine free results, one of the most difficult outcomes to achieve, at 2 and 4 hours across multiple studies.

Treximet: Sustained Efficacy

Treximet provided superior sustained pain relief (2-24 hours) versus sumatriptan 85 mg, naproxen sodium 500 mg, and placebo in pivotal efficacy trials of moderate-severe migraine pain.[15,16] *Treximet* also provided superior sustained pain-free results (2-24 hours) across multiple studies evaluating treatment of moderate-to-severe migraine pain or mild pain.[15,16] [8,9,17,18,19,20,21,22] In addition, in all of these studies, the use of rescue medication was significantly reduced in patients taking *Treximet*.

Treximet: Consistency of Response

In two studies evaluating consistency of response, *Treximet* demonstrated consistent efficacy across multiple attacks.[19,20] Individual patients also consistently responded to *Treximet* across attacks.

Treximet: Efficacy in Patients with Poor Response to Short-Acting Triptans

In two studies evaluating patients who reported poor response or intolerance to previous treatment with short-acting triptans, *Treximet* provided superior efficacy results versus placebo across a variety of endpoints.[8,9]

Treximet: Economic Benefit

A Pharmacy Budget Impact Model (PBIM) demonstrates that the addition of *Treximet* to the second-tier of a health plan's formulary ranges from budget neutrality to modest savings across a range of varying assumptions.[25] The cost savings is largely a function of superior response, lower recurrence, and sustained pain-free rates.

Treximet: Safety

Treximet contains a boxed warning for cardiovascular and gastrointestinal risk. Please see complete product prescribing information for more information.

In clinical trials, *Treximet* was generally well-tolerated.[15,16] [8,9,17,18] [19,20,21,22] The most common adverse events with *Treximet* are dizziness (4%), somnolence (3%), nausea (3%), chest discomfort/chest pain (3%), neck/throat, jaw pain/tightness/pressure (3%), paresthesia (2%), dyspepsia (2%), and dry mouth (2%).[26]

Treximet has also been evaluated in a 12-month long-term safety trial.[23] The overall safety population included 565 patients who treated 24,485 attacks. The most common adverse events were nausea (6%), dyspepsia (2%), dizziness (3%), muscle tightness (3%), upper abdominal pain (2%), paresthesia (2%), and chest discomfort (2%). One drug-related cardiovascular serious adverse event with *Treximet* was reported in the study.

2. DISEASE DESCRIPTION

2.1 Epidemiology of Migraine

Epidemiology of Migraine

Migraine is a common and often debilitating neurobiological disorder. Migraine is most likely to affect the working-age individual and is associated with substantial costs to both the employer and to the healthcare system. [27] [28] [29] Migraine costs American employers $13 billion per year due to missed work and reduced productivity. [28] An estimated 157 million workdays are lost annually because of the pain and associated symptoms of migraine.

Over the past decade, many new treatments for migraine have become available, and the awareness of migraine has improved. Some studies suggest that the prevalence of migraine may be increasing. [30] [31] [32]

2.2 Pathophysiology of Migraine

Migraine Pathophysiology

Migraine may start in the cerebral cortex, the outer layer of the brain, consisting of nerve cells and the pathways that connect them. This extensive gray matter mass is largely responsible for sensation, voluntary muscle movement, thought, reasoning, and higher brain functions such as memory.

Cortical hyperexcitability forms the basis of migraine susceptibility.[33] The onset of migraine can be initiated by a variety of internal and external triggers, which may lead to cortical spreading depression.[34] Cortical spreading depression is a wave of depolarization that propagates slowly across the cortex, depressing neuronal activity for a few minutes and transiently reducing cerebral blood flow.[35] Cortical spreading depression is further believed to stimulate the central nervous system and initiate a cascade of events, including the activation of trigeminal sensory fibers surrounding cerebral and meningeal blood vessels.[1,36]

During activation of trigeminal sensory fibers surrounding cerebral and meningeal blood vessels, the stimulated nerve fibers release neurochemicals, such as calcitonin gene related peptide (CGRP), substance P, nitrous oxide, and cytokines.[1,36] The release of the these neurochemicals results in a secondary inflammatory response, which includes the production of prostaglandins through a conversion of arachidonic acid by cyclooxygenase.[37] CGRP and the inflammation caused by prostaglandins in turn act upon local blood vessels causing vasodilation and inflammation.[2,38]

These responses activate meningeal pain receptors called nociceptors, which then transmit the signals to the trigeminal ganglion and centrally to the trigeminal nucleus caudalis (TNC).[1,2] The three divisions of the trigeminal nerve come together in the trigeminal ganglion. From there, the trigeminal nerve root continues back towards the side of the brain stem, and inserts into the pons. Within the brain stem, the signals traveling through the trigeminal nerve reach specialized clusters of neurons called the TNC. From the TNC, the signals travel to higher brain centers, including the thalamus and cerebral cortex.[1] [39] When the signal reaches the cerebral cortex, the patient first experiences the sensation of pain.[1] [40] Therefore, the following mechanisms have been initiated prior to pain perception (before most patients take their medication): neuroactive substances released, initiation of arachidonic cascade, vasodilation and inflammation, activation of nociceptors (pain transmission), signals transmitted centrally to TNC, and signals traveled to higher brain centers, including the thalamus and cerebral cortex. [40]

In addition, prolonged stimulation of the trigeminal nerves occurs early in the migraine process and results in peripheral sensitization.[41] Peripheral sensitization is a reduction in threshold and an increase in responsiveness of the peripheral nociceptors.[42] Following peripheral sensitization, continuous stimulation of the trigeminal ganglion results in activation of the TNC and surrounding glial cells.[1,2]

Glial cells, which surround neurons and were previously believed only to provide nutritional support, are now believed to also play a role in neuronal modulation.[43] Once activated, glial cells release prostaglandins. These prostaglandins are believed to contribute to the stimulation of the TNC, independent of signals from the trigeminal ganglion.[43,44,45]

Prolonged stimulation of the TNC results in continuous firing by the TNC independent of any signals coming from the periphery; this creates a self-sustaining loop called central sensitization. The presence of central sensitization is associated with more refractory migraines where a sustained pain-free response is harder to achieve.[37,41] Cutaneous allodynia is a marker for central sensitization and results in patients often avoiding certain activities including: combing hair, shaving, wearing eyeglasses, wearing jewelry, or resting the face on the pillow on the migraine side. [46] [47]

Activation of the TNC may also result in referral of pain to various locations along the trigeminocervical network including the three branches of the trigeminal nerve [ophthalmic branch (V1), the maxillary branch (V2), and the mandibular branch (V3)] as well as the sensory nerves for the posterior head and neck (C2, C3, and C4).[48] Pain may be perceived on one or both sides of the head, around the eyes or sinuses, and in the posterior area of the head and neck.[49] Through connections with the superior salivatory nucleus, activation of the TNC may additionally cause reflex cranial parasympathetic activation resulting in sinus-like symptoms such as rhinorrhea, congestion and lacrimation.[1] [50]

The pathophysiology of migraine is now believed to involve multiple mechanisms such as vasodilation, inflammation, activation of pain receptors (nociception), peripheral and central sensitization, and referred pain.

2.3 Clinical Presentation of Migraine

Clinical Presentation of Migraine

Diagnostic Criteria of Migraine

According to the International Headache Society (IHS) diagnostic criteria for migraine headaches, the following symptoms must be present and not attributed to another cause.(51)

- At least two of these symptoms:
  - pain on one side of the head,
  - moderate to severe pain,
  - throbbing pain,
  - worsening of pain when moving or bending
- At least one of these associated symptoms:
  - nausea or vomiting,
  - sensitivity to light and sound

Symptoms of migraine can vary from attack to attack in the same person and different people may exhibit different symptoms. The failure to diagnose migraines may be due in part to a lack of understanding of migraine and the similarity in symptoms to other conditions. One study evaluating headache diagnosis patterns revealed that 94% of patients who consulted a primary care physician for headaches met International Headache Society (IHS) criteria for migraine or probable migraine. (52) The same study found that nearly 90% of self-diagnosed tension/stress headache patients met IHS criteria for migraine or probable migraine. In the American Migraine Study II, almost two-thirds of all undiagnosed migraine sufferers were misdiagnosed with either a tension-type headache or sinus headache. (53)

Sinus-Like Presentation of Migraine

Many cranial autonomic symptoms such as nasal congestion, rhinorrhea, and lacrimation commonly interpreted as sinus symptoms may occur in migraine. Among 177 interviewed migraineurs (46%) reported at least one nasal (nasal congestion and/or rhinorrhea) or ocular (lacrimation, conjunctival injection, and/or eyelid edema) symptom with their migraine. (54) Of this 46%, 37 patients (46%) reported both nasal and ocular symptoms. Patients reported that headaches with autonomic symptoms were more severe and unilateral than headaches without these symptoms.

Tension-Type Presentation of Migraine

According to IHS criteria, tension-type headache (TTH) is usually manifested as bilateral head pain with a non pulsating quality that does not worsen with physical activity. (55) There is no nausea, but photophobia or phonophobia may be present. However, migraine pain may also be bilateral and non-pulsating. In the American Migraine Study II, 41% of individuals meeting IHS criteria for migraine reported bilateral pain with their headaches. Non-pulsating pain has also been reported in over 50% of migraineurs. (53)

A chart review of 412 patients with IHS diagnosis of migraine (1.1 or 1.2) and no other headache diagnoses confirmed that migraine patients often experience symptoms and characteristics commonly associated with TTH.(56) Tension like symptoms or characteristics were reported with the following frequencies: stiffness or tightness in neck and shoulders (51%), occipital/cervical distribution (59%), tenderness of neck muscles (37%), and headaches due to tension or stress (57%). Approximately 9 of 10 patients reported one or more characteristics associated with TTH.

3. PLACE IN THERAPY

3.1 Unmet Needs and Opportunity for Improvement

Migraine is a Multimechanistic Disease

Current understanding of the pathophysiology of migraine suggests that there are multiple mechanisms involved, including neurochemical release, vasodilation, inflammation, and prostaglandin production.[1,2,3] Individual migraine-specific monotherapies address some, but not all of the multiple components of migraine.

Acute Migraine Therapy: Stratified Care Proven Superior to Step Care

Available guidelines recommend various treatment options for selecting and sequencing acute migraine treatments. Of these options, results of the Disability In Strategies of Care (DISC) Study showed that stratified care provided a significantly greater response (52.7%) across 6 attacks compared with step care across attacks (40.6%) and step care within attacks (36.4%) ($P<0.01$) [4]. In addition, disability time was significantly less for stratified care compared with the step care approach.

Opportunity for Improvement: Patients are Currently Selecting Step Care Approach FOR Managing Migraine

Despite the fact that stratified care has been proven superior to a step care approach, patients with access to multiple acute migraine therapies are practicing step care. A survey of 425 migraineurs showed that 71% used multiple medications to treat their migraines.[5] Over half reported using a step care approach within attack, and 17% used a rescue medication. Similarly, in a managed care population of migraineurs who had previously treated an attack with a triptan plus an NSAID, approximately one quarter chose to treat their next attack with an NSAID first, followed by a triptan later. [6] Patients with access to multiple acute migraine treatments are missing an opportunity for improved response and decreased disability by choosing a step care approach, and may be doing so without the knowledge of their healthcare provider.

Opportunity for Improvement: Use of Opioids/Narcotics Is Prevalent

Data also show that the use of opioids and narcotics is extensive. Even though guidelines suggest otherwise, narcotics continue to be used often for the treatment of migraine. An analysis of migraineurs in a large managed care database found that 38% of migraine patients compared to 24% for matched controls had filled a narcotic.[7] Alarmingly, 7% of migraine cases filled only narcotic medications with no fills for other medications commonly used to treat headache. Although possibly inexpensive in the short-term, the potential for progression to medication overuse headache, ER visits, and long-term costs is great.

Opportunity for Improvement: Current Therapies Don't Always Work and Result in Redosing or Use of Rescue

Another shortfall of current therapies includes inadequate response. Baseline demographics from two studies evaluating patients refractory to short-acting triptans showed that the most common reason for study enrollment was lack of efficacy with prior therapy. [57]

Opportunity for Improvement: Dissatisfaction with Current Therapy

At screening for a long-term safety study, only about half of patients considered themselves to be satisfied or very satisfied by their previous treatment.[10] Not surprisingly, a study by Bigal, et al showed that 80% of patients would be willing to try another acute migraine therapy. [11] Reasons cited for dissatisfaction included recurrence, need for redosing, lack of ability to function/return to work quickly, and onset of effect.

4. PRODUCT DESCRIPTION

4.1 Generic Name, Brand Name and Therapeutic Class

a. Generic Name: sumatripan and naproxen sodium

b. Brand Name: *Treximet*™

c. Therapeutic Class: 5-$HT_{1B/1D}$ Agonist/Nonsteroidal Anti-inflammatory Drug (NSAID)

4.2 Dosage Forms and Package Sizes

Treximet contains 119 mg of sumatriptan succinate equivalent to 85 mg of sumatriptan and 500 mg of naproxen sodium and is supplied as blue film coated tablets debossed on one side with GS YYG in compact containers of 9 tablets with a specially formulated, non removable desiccant.

4.3 NDC for All Formulations

NDC 0173-0750-00

4.4 AHFS or Other Drug Classification

28:32.28 Selective Serotonin Agonists

4.5 FDA Approved and Other Studied Indications

Refer to Enclosed Prescribing Information.

4.6 Use in Special Populations

Hepatic Impairment

Because *Treximet* is a fixed-dose combination that cannot be adjusted for this patient population, it is contraindicated in patients with hepatic impairment.[26] The effect of hepatic impairment on the pharmacokinetics of *Treximet* has not been studied. Sumatriptan is contraindicated in patients with severe hepatic impairment and the dose is limited to 50 mg in patients with liver disease.

A patient with symptoms and/or signs suggesting liver dysfunction or in whom an abnormal liver test has occurred should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with *Treximet*. Borderline elevations of 1 or more liver tests may occur in up to 15% of patients who take nonsteroidal antiinflammatory (NSAID)-containing products. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Notable (3 times the upper limit of normal) elevations of SGPT (ALT) or SGOT (AST) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis, and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with *Treximet*. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash), *Treximet* should be discontinued.

Renal Impairment

Background

Minimal change in clinical effect would be expected with regard to sumatriptan as it is largely metabolized to an inactive substance.[26] Since naproxen and its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment.

Clinical Information

Treximet is not recommended for use in patients with creatinine clearance (CrCl) less than 30 mL/min.[26] The effect of renal impairment on the pharmacokinetics of *Treximet* has not been studied. Caution is recommended in patients with preexisting kidney disease or dehydration.

Long-term administration of nonsteroidal anti-inflammatory drugs (NSAIDs) has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and

angiotension-converting enzyme (ACE) inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Naproxen and its metabolites are eliminated primarily by the kidneys; therefore, *Treximet* should be used with caution in patients with significantly impaired renal function, and monitoring of serum creatinine and/or creatinine clearance is advised in these patients. No information is available from controlled clinical studies regarding the use of *Treximet* in patients with advanced renal disease.

Pharmacokinetic Considerations

The clearance of naproxen is 0.13 mL/min/kg.[26] Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-0-desmethyl naproxen (less than 1%), or their conjugates (66% to 92%). The plasma half-life of the naproxen anion in humans is approximately 19 hours. The corresponding half-lives of both metabolites and conjugates of naproxen are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. In patients with renal failure, metabolites may accumulate.

Pregnancy

Treximet is Pregnancy Category C. [26] There are no adequate and well-controlled studies in pregnant women. Inhibitors of prostaglandin synthesis (including naproxen) are known to delay parturition. Because of this and the known effects of drugs of this class on the human fetal cardiovascular system (closure of the ductus arteriosus), use of *Treximet* during third trimester should be avoided. *Treximet* should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

In developmental toxicity studies in rabbits, oral treatment with sumatriptan combined with naproxen sodium (5/9, 25/45, or 50/90 mg/kg/day sumatriptan/naproxen sodium) or each drug alone (50/0 or 0/90 mg/kg/day sumatriptan/naproxen sodium) resulted in decreased fetal body weight in all treated groups and in increased embryofetal death at the highest dose of naproxen, alone and in combination with sumatriptan. Naproxen sodium, alone and in combination with sumatriptan, increased the total incidences of fetal abnormalities at all doses and increased the incidences of specific malformations (cardiac interventricular septal defect in the 50/90 mg/kg/day group, fused caudal vertebrae in the 50/0 and 0/90 mg/kg/day groups) and variations (absent intermediate lobe of the lung, irregular ossification of the skull, incompletely ossified sternal centra) in the 50/0 and 0/90 mg/kg/day groups. A no-effect dose for development toxicity in rabbits was not established. The lowest effect dose was 5/9 mg/kg/day sumatriptan/naproxen sodium, which was associated with plasma exposures (AUC) to sumatriptan and naproxen that were 1.4 and 0.14 times, respectively, those attained at the maximum recommended human oral daily dose of 85 mg sumatriptan and 500 mg naproxen sodium.

In previous developmental toxicity studies in rats and rabbits, oral treatment with sumatriptan was associated with embryolethality, fetal abnormalities, and pup mortality. Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in an increased incidence of fetal blood vessel (cervicothoracic and umbilical) abnormalities and decreased pup survival at doses of 250 mg/kg/day or higher. The highest no effect dose was approximately 60 mg/kg/day, which is approximately 7 times the recommended human oral daily dose of 85 mg sumatriptan on a mg/m^2 basis. Oral treatment of pregnant rabbits with sumatriptan during the period of organogenesis resulted in an increased incidence of cervicothoracic vascular and skeletal abnormalities at a dose of 50 mg/kg/day and embryolethality at 100 mg/kg/day. The highest no effect dose for embryotoxicity in rabbits was 15 mg/kg/day, or approximately 3 times the recommended human oral daily dose of 85 mg sumatriptan on a mg/m^2 basis.

To monitor fetal outcomes of pregnant women exposed to *Treximet*, GlaxoSmithKline maintains a *Treximet* Pregnancy Registry. Physicians are encouraged to register patients as soon as possible after they become pregnant and (if possible) before the outcome of the pregnancy is known by calling (800) 336-2176.

Lactation

Both active components of *Treximet*, sumatriptan and naproxen sodium, have been reported to be excreted in human breast milk.[26] Because of the possible adverse effects of these drugs on neonates, use of *Treximet* in nursing mothers should be avoided.

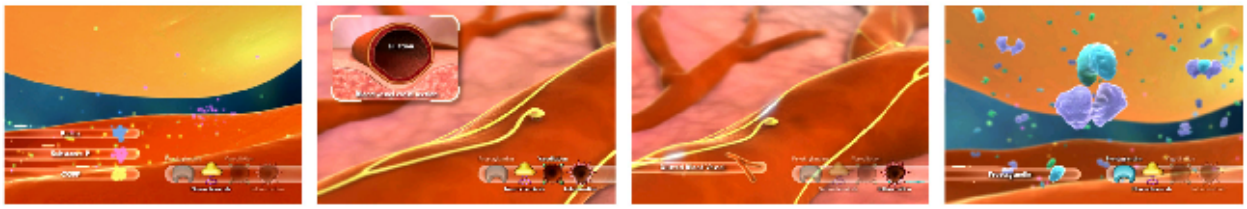
4.7 Pharmacology

Treximet: mechanism of action

Recent research indicates that migraine pathophysiology involves multiple mechanisms.[1,2,3] These mechanisms include: neurochemical release, vasodilation, prostaglandin production, and inflammation. In turn, these mechanisms lead to the associated events of pain transmission and referred pain, parasympathetic activation, and peripheral and central sensitization. *Treximet* contains 85 mg of sumatriptan, which is a 5 $HT_{1B/1D}$ receptor agonist, formulated with RT technology; it also contains 500 mg of naproxen sodium, a non-steroidal anti-inflammatory drug (NSAID). [26] These agents contribute to the relief of migraine through pharmacologically different mechanisms of action (see Figure 1).

Figure 1. *Treximet* Targets the Multiple Mechanisms of Migraine [3,58]

Proposed Mechanism	TREXIMET
Inhibits neurochemical release	X
Reverses vasodilation	X
Inhibits prostaglandin production	X
Directly reduces inflammation	X



Neurochemical release | Vasodilation | Inflammation | Prostaglandin production

Treximet: Sumatriptan Component

The sumatriptan component of *Treximet* acts to relieve migraine through 5-$HT_{1B/1D}$ agonist activity.[26] The 5-HT_{1B} receptors are located on intracranial blood vessels and central nervous system (CNS) neurons. The 5-HT_{1D} receptors are located on CNS neurons and trigeminal nerve endings. [59,60] Sumatriptan has only weak affinity for $5HT_{1A}$, $5HT_{5A}$, and $5HT_7$ receptors and no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at $5HT_2$, $5HT_3$, or $5HT_4$ receptor subtypes or at $alpha_1$, $alpha_2$, or beta-adrenergic; $dopamine_1$; $dopamine_2$; muscarinic; or benzodiazepine receptors.[26]

Sumatriptan constricts extracerebral intracranial vessels, inhibits trigeminal neurons, and blocks transmission in the trigeminal nucleus.[61] Neuropeptide release is likely also inhibited. Neurogenic inflammation within the meningeal vasculature is characterized by plasma protein extravasation, vasodilation, and mast cell degranulation, and is theorized to be mediated by neuropeptide release from trigeminal sensory fibers. Sumatriptan and other clinically effective migraine agents block dural extravasation.

Treximet: Naproxen Sodium Component

Naproxen sodium is a long-acting NSAID with analgesic and antipyretic properties.[26,37] It is a non-selective inhibitor of cyclooxygenase 1 and 2 (COX-1 and COX-2). Its actions result in decreases in prostaglandin synthesis and leukocyte activation. NSAIDs have been shown to block neurogenic dural extravasation and to block trigeminal sensitization.[62] NSAIDs may also attenuate central sensory processing in the trigeminal nucleus caudalis as one mechanism of demonstrated benefit in migraine.

Treximet Targets the Multiple Mechanisms of Migraine

At the onset of migraine, the trigeminal nerves surrounding blood vessels of the brain and meninges become activated and release various neurochemicals including calcitonin gene related peptide (CGRP), substance P, and kinins.(36) (1) The sumatriptan component of *Treximet* inhibits the release of these neurochemicals from the trigeminal nerve terminals, inhibiting their vasodilatory and pro-inflammatory effects. (63) (64) (65) (66,67,68) In addition, the sumatriptan component of *Treximet* directly activates 5-HT_{1B} (vascular) receptors located on the smooth muscle in blood vessels, thereby reversing vasodilation. (26) (40) (69) (63)

The release of neurochemicals from trigeminal nerve terminals during migraine assists in the formation of prostaglandins.(70) (37) Prostaglandins are autocrine and paracrine lipid mediators produced by the conversion of arachadonic acid (derived from cell wall phospholipids) by COX-1 and COX-2.(1) Prostaglandins contribute to vasodilation and inflammation, playing an important role in maintaining headache pain, and have been implicated in sensitizing neurons involved in nociceptive transmission during migraine.(13) Naproxen sodium inhibits the synthesis of inflammatory mediators.(26)

Neurochemicals appear to be released at different time points during a migraine attack.(13) An experimental model of nitroglycerin-induced headache showed that calcitonin gene-related peptide (CGRP) and neurokinin A (NKA) reach their highest levels during the first hour of a migraine attack, while prostaglandin E_2, and to a less extent 6-keto PGF1α [a stable metabolite of prostacyclin (PGI2)] levels, reach a peak during the second hour with concentrations maintained through hours 4 and 6 from attack onset. In turn, prostaglandins regulate the release and modify the actions of these neurochemicals. Activation of the receptors for prostaglandins D_2 (PGD_2), E_2 (PGE_2) and prostacyclin (PGI_2) causes release of CGRP from trigeminal neurons.(71) Arterioles of the brain are strongly responsive to prostaglandins, which are important mediators of cerebral blood flow under normal and abnormal conditions. PGs D_2, E_2, G_2, and I_2 have been shown to be potent dilators of cerebral arterioles.(72) PGD_2 appears responsible for the intense vasodilation and headache that follow administration of pharmacological doses of vitamin B.(73) COX-2 has been shown to be dramatically upregulated after cortical spreading depression (CSD), triggering an increase in CNS PG production. Increased PG production, particularly PGD_2, following CSD can induce non-REM sleep and this may account for the sleepiness sometimes associated with this neurologic event in migraineurs.(74) NSAIDS may mitigate or reverse many of the processes driven by the increased prostaglandin production associated with migraine.

Peripheral Sensitization

During migraine, neurochemical release, vasodilation, prostaglandin production, and inflammation can result in the hypersensitivity of trigeminal pain receptors.(1) Normal activation of these pain receptors (nociceptors) transmits peripheral pain signals via the trigeminal nerve centrally to the trigeminal nucleus caudalis (TNC) in the brainstem.(1,2) The TNC then transmits these pain signals to the thalamus and cerebral cortex.(1,68) It is when the cortex is stimulated that the patient first experiences the sensation of pain. (1,40) Continued activation of the peripheral nociceptors by the ongoing stimulus of a migraine attack produces hypersensitivity of the trigeminal nerve. This heightened sensitivity of the trigeminal nerve is termed “peripheral sensitization”. (66) (75) Hypersensitized trigeminal pain receptors can be activated by normally innocuous stimuli , therefore clinically, actions such as simple head movements and coughing may result in pain. (13)

Central Sensitization

Prolonged stimulation of the TNC during a migraine attack may result in of the TNC, termed "central sensitization".(41) (75) Central sensitization results in TNC activity that is no longer dependent on incoming impulses from the trigeminal nerve for its maintenance. Nitric oxide (NO) and prostaglandins have been shown to be key mediators involved in the induction and maintenance of this state, and NO, PGE_2, and glutamate mutually potentiate each other’s release.(76) Addtionally, neuron-supportive cells called glial cells contribute to this sensitization by releasing prostaglandins along with other inflammatory mediators.(43,44,45) The sumatriptan component of *Treximet* inhibits pain transmissions centrally between the trigeminal nerve and the TNC, thereby reducing the stimulus to the TNC. (75) By reducing pain signals from the peripheral pain nocioceptors to the TNC, *Treximet* may help prevent the onset of central sensitization, if administered early in the course of a migraine.(41) Pre-clinical research suggests that naproxen, a component of *Treximet*, may reverse already established central sensitization by inhibiting the

release of prostaglandins in the TNC.[77] The trigeminal nerve sends sensory signals to the TNC not only from the meningeal branches surrounding blood vessels, but also from the branches [ophthalmic (V1), maxillary (V2), and mandibular (V3)] that innervate the face. Additionally, the TNC receives input from the sensory fibers of the cervical nerves that innervate the upper neck and back of the head. The convergence of these multiple pathways at the TNC may explain why migraine pain can be referred to the face and upper neck.[78] *Treximet* helps halt this referred pain by interrupting pain impulses to the TNC.[41]

Treximet: Distinct Pharmacokinetic Profile to Address Early and Late Phases of Migraine

The RT technology used in the formulation of the sumatriptan component of *Treximet* enhances the dispersion, dissolution, and absorption of sumatriptan resulting in the rapid development of sumatriptan blood levels.[79] The sumatriptan administered as *Treximet* reaches a time to maximum concentration sooner as compared to *Imitrex* 100 mg formulated with RT technology.[26] Naproxen sodium, as a component of *Treximet* exhibits lower peak levels and a delayed time to maximum concentration compared to naproxen sodium 550 mg.[26] Together as *Treximet* these agents contribute to the relief of migraine through pharmacologically different mechanisms of action and a distinct pharmacokinetic profile to effectively address early and late stages of the migraine process.

4.8 Pharmacokinetics/Pharmacodynamics

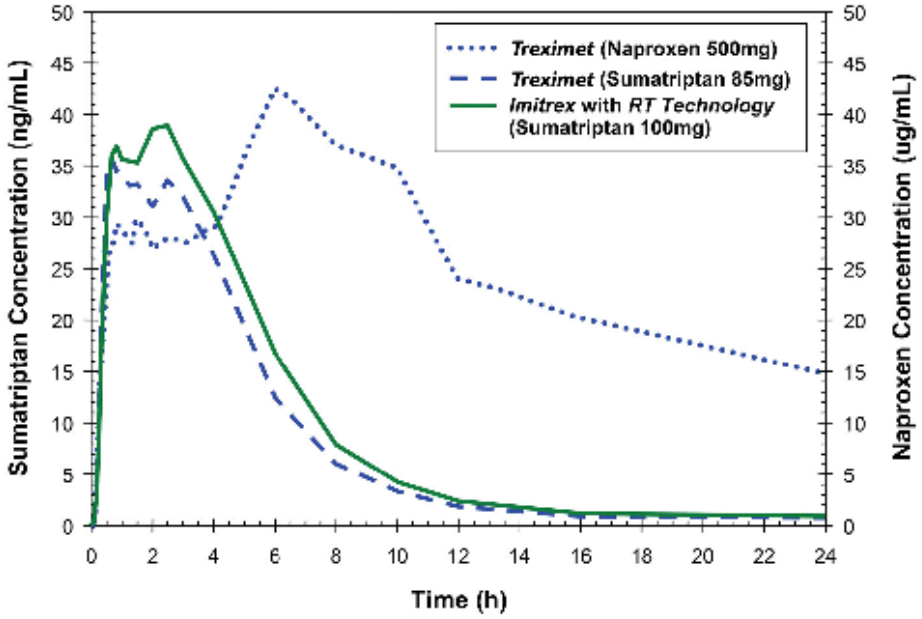
Pharmacokinetic Profile of Treximet

Absorption

The area under the curve (AUC) values for sumatriptan and for naproxen following a single dose of *Treximet* are similar to those following a single dose of *Imitrex* 100 mg or naproxen sodium 550 mg.[26] [80] Bioavailability of sumatriptan is approximately 15%, primarily due to presystemic (first pass) metabolism and partly due to incomplete absorption.[26] Naproxen is rapidly and completely absorbed from the gastrointestinal tract with an *in vivo* bioavailability of 95%. Food had no significant effect on the bioavailability of sumatriptan or naproxen administered as *Treximet*, but slightly delayed the T_{max} of sumatriptan (by about 0.6 hour).[26,81]

The mean C_{max} for sumatriptan achieved following a single dose of *Treximet* is similar to that following a single dose of *Imitrex* Tablets 100 mg (see Figure 2).[12,26] The median sumatriptan T_{max} is only slightly different (1 hour for *Treximet* and 1.5 hours for *Imitrex*).[12,26,80,81,82] The C_{max} for naproxen following administration of *Treximet* occurs at approximately 5 hours (median, range 0.3 to 12 hours).[80,81,82]. The C_{max} for naproxen is approximately 36% lower, and the T_{max} occurs approximately 4 hours later when naproxen was administered as *Treximet* compared to naproxen sodium 550 mg tablets.[26,80] In a crossover study in 16 patients, the pharmacokinetics of both components administered as *Treximet* were similar during a migraine attack and during a migraine free period.[83]

Figure 2. Sumatriptan and Naproxen Concentrations 0-24 Hours[12]



Theoretical Rationale for Distinct Pharmacokinetic Profile of *Treximet*

While it is unknown why the pharmacokinetic profiles of sumatriptan and naproxen within *Treximet* are distinct, several theories exist. *Treximet* is a bilayer formulation, therefore, the sumatriptan and naproxen layers share a common side. Based on the formulation and the results of an *in vitro* evaluation, it is theorized that the thin layer of sumatriptan residual on the tablet may affect release of the naproxen component, contributing to the delayed absorption.[84] The *in vitro* study of *Treximet* Tablets in simulated gastric fluid show that a residual amount of sumatriptan remains on the naproxen side of theTreximet tablet in simulated gastric fluid at 5 (5.3%) and 7.5 (5.1%) minutes.

Secondly, it is theorized that the increased tablet weight of *Treximet* (1075 mg) as compared to *Imitrex* 100 mg (350 mg), may affect the tablet transit through the stomach. Specifically, the heavier tablet is more likely to pass through the fundus to the pylorus near the small intestine, the presumed site of absorption, resulting in faster absorption of sumatriptan. Thirdly, these findings taken together with the known effect of triptans reducing gastric motility, result in the blunted and delayed absorption of naproxen.[85]

Lastly, potential interactions based on the acidic properites of sumatriptan and basic properties of naproxen sodium, cannot be ruled out. Further evaluation is needed to fully understand the reason for the distinct pharmacokinetic profile of *Treximet*.

Distribution

The volume of distribution of sumatriptan is 2.4 L/kg.[26] Plasma protein binding is 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated, but would be expected to be minor, given the low protein binding. The volume of distribution of naproxen is 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin bound. At doses of naproxen greater than 500 mg/day, there is a less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough C_{ss} 36.5, 49.2, and 56.4 mg/L with 500; 1,000; and 1,500 mg daily doses of naproxen, respectively). However, the concentration of unbound naproxen continues to increase proportionally to dose.

Metabolism

Most of a radiolabeled dose of sumatriptan excreted in the urine is the major metabolite indole acetic acid (IAA) or the IAA glucuronide, both of which are inactive.[26] Three percent of the dose can be recovered as unchanged sumatriptan. *In vitro* studies with human microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme, and inhibitors of that

enzyme may alter sumatriptan pharmacokinetics to increase systemic exposure. No significant effect was seen with an MAO-B inhibitor. Naproxen is extensively metabolized to 6-0-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes.

Elimination

Radiolabeled ^{14}C-sumatriptan administered orally is largely renally excreted (about 60%), with about 40% found in the feces.(26) The elimination half-life of sumatriptan is approximately 2 hours. The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-0-desmethyl naproxen (less than 1%), or their conjugates (66% to 92%). The plasma half-life of the naproxen anion in humans is approximately 19 hours. The corresponding half-lives of both metabolites and conjugates of naproxen are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. In patients with renal failure, metabolites may accumulate.

Pharmacokinetics of Treximet Inside and Outside of a Migraine Attack

A non-randomized, open-label, one-sequence, cross-over study of 18 adult volunteers evaluated the pharmacokinetics of sumatriptan succinate and naproxen sodium given as a single dose of *Treximet* during and outside of a migraine attack.(83) The two treatment periods were separated by at least an eight day washout period. Blood samples for determination of sumatriptan and naproxen plasma concentrations were collected pre-dosing and at multiple timepoints after dosing.

No significant differences in area under the curve ($AUC_{0\text{-}inf}$ and $AUC_{0\text{-}2}$ [sumatriptan only]), maximum concentration (C_{max}), time to maximum concentration (T_{max}), or half-life ($t_{1/2}$) were observed for sumatriptan and naproxen sodium, administered as *Treximet*, during or outside of a migraine attack. The ratios and confidence intervals of AUC values, C_{max} and $t_{1/2}$ were within the accepted bioequivalence limits of 0.8 to 1.25 for both naproxen sodium and sumatriptan for each of these measures. There was no difference in the median T_{max} values for sumatriptan or naproxen and the 95% confidence interval for the median difference included zero.

Adverse events observed with *Treximet* during and outside of a migraine attack were classified as mild. The most frequently reported drug-related adverse event was somnolence, occurring in two patients in each treatment group. No serious adverse events were reported.

Pharmacokinetics of Sumatriptan 85 mg versus 100 mg

Open-Label Pharmacokinetic Study

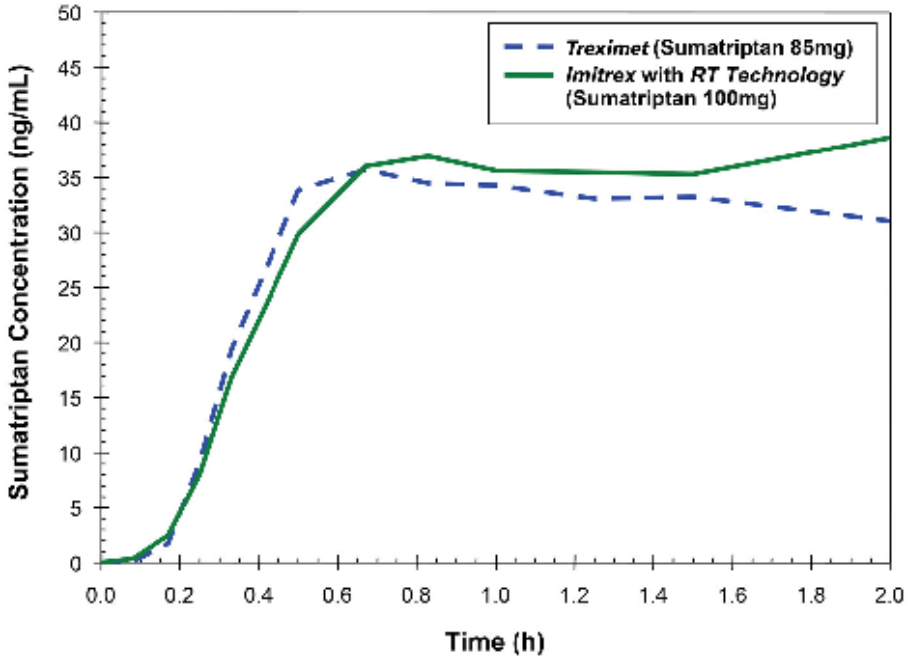
A single-center, randomized, open-label, single-dose, 2-period crossover pharmacokinetic study in healthy adult volunteers (N = 32) compared sumatriptan bioavailability following administration of a single *Treximet* tablet and a single *Imitrex* 100 mg tablet formulated with *RT Technology*.(12) Tolerability (including cardiovascular effects through 10 hours post-dose) and naproxen pharmacokinetics were also evaluated. Sumatriptan and naproxen concentrations were analyzed from serial blood samples. Serial blood pressure measurements and 5-lead continuous telemetry were performed 1 hour prior to dosing and through 10 hours post-dose.

Sumatriptan early exposure ($AUC_{0\text{-}2}$) and peak concentrations (C_{max}) were similar following administration of *Treximet* and *Imitrex* 100 mg formulated with *RT Technology* (Table 1 and Figure 3).(12) While sumatriptan C_{max} and $AUC_{0\text{-}2}$ were decreased, on average, by 10% and 4%, respectively, for *Treximet* relative to *Imitrex*, the 90% confidence intervals (CIs) were within the 0.80 – 1.25 limits used to establish bioequivalence. Similarly there was a 15% decrease in a sumatriptan $AUC_{0\text{-}\infty}$ for *Treximet* compared to *Imitrex* 100 mg, due to the relative difference in sumatriptan doses but the 90% CIs were within the 0.80 – 1.25 limits. The median sumatriptan T_{max} is only slightly different (1 hour for *Treximet* and 1.5 hours for *Imitrex*).(12,26)

Table 1. Sumatriptan Pharmacokinetic Parameters*(12)

Treatment	N	AUC_{0-2}(ng·hr/mL)	$AUC_{0-\infty}$(ng·hr/mL)	C_{max}(ng/mL)	t_{max}(hr)
Treximet	32	52.8 (36.6)	192 (31.2)†	44.3 (27.9)	0.830 (0.35-4)
Imitrex	32	54.8 (39.5)	230 (33.2)	49.4 (36.2)	1.50 (0.42-6)
*Data presented as geometric mean (CV%); t_{max} presented as median (range); †n = 28					

Figure 3. Sumatriptan Concentrations: 0-2 Hours



4.9 Contraindications

Refer to Enclosed Prescribing Information.

4.10 Warnings/Precautions

Refer to Enclosed Prescribing Information.

4.11 Adverse Events

Refer to Enclosed Prescribing Information.

4.12 Other Clinical Considerations

Refer to Enclosed Prescribing Information.

4.13 Drug/Food/Disease Interactions

The Effect of Food on the Pharmacokinetics of Treximet

Treximet may be administered without regard to food.(26)

A randomized, open-label, single-center, three-way cross-over study examined the effects of fed and fasted states on a single-dose of *Treximet*.(81) Twenty-four healthy volunteers, aged 18 to 55 years, were randomized to one of six treatment sequences comprised of three treatments: *Treximet* (fasted), *Treximet* (fed), and sumatriptan (fasted). The fed treatment group received study drug 30 minutes after ingesting a high fat meal (800–1000 calories, with 50% of calories from fat) while the other treatment groups received study drug in the fasted state. Each treatment was separated by a washout period of at least eight days. Blood samples for the determination of naproxen and sumatriptan plasma concentrations were collected pre-dose and at multiple timepoints after dosing.

The administration of food did not significantly affect the area under the curve ($AUC_{0\text{-}inf}$), maximum concentration (C_{max}), or half-life ($t_{1/2}$) of naproxen sodium or sumatriptan given as *Treximet*. The parameter ratios (fasted/fed) and 90% confidence intervals (CI) were within the accepted bioequivalence limits of 0.8 to 1.25 for both naproxen sodium and sumatriptan. There was no difference in the median T_{max} values for naproxen. The difference in the median values for sumatriptan T_{max} was 0.67 hour. The 95% CI (0.25 to 1.08) did not include zero indicating sumatriptan T_{max} was delayed, on average, by 40 minutes (range 15 to 65 minutes) when administered after a high fat meal.

Adverse events observed with *Treximet* (fasted and fed) were all classified as mild, with the exception of one nausea event classified as moderate. The most frequent drug-related adverse event was dizziness, occurring in 23% the *Treximet* (fasted) subjects compared to 13% each in the *Treximet* (fed) and sumatriptan 85 mg groups. One subject was discontinued due to continuous elevated blood pressure. No serious adverse events were reported.

Concomitant Use with Naproxen Sodium

Treximet and other naproxen-containing products should not be used concomitantly since they all circulate in the plasma as the naproxen anion.[26]

In most clinical studies evaluating the safety and efficacy of *Treximet*, nonsteroidal antiinflammatory drugs (except doses of aspirin ≤ 325 mg per day being used for cardiovascular prophylaxis) were not to be taken within 24 hours prior to or following treatment with study drug.[15,16,17,18,86]

In two randomized, double-blind, multi-center, placebo-controlled studies that evaluated the efficacy and safety of *Treximet* during the mild pain phase of acute migraine, rescue medications, including naproxen sodium, were allowed beginning 2 hours after dosing with *Treximet*. The recommended rescue medication regimen was two naproxen sodium 220 mg tablets, then one additional tablet (220 mg) six hours later if needed, not to exceed three naproxen sodium 220 mg tablets in a 24 hour period. The efficacy and safety of naproxen sodium taken as rescue medication was not evaluated in these studies.[19,20]

Concomitant Use with Monoamine-Oxidase (MAO)-A Inhibitors

Concurrent administration of monoamine oxidase (MAO)-A inhibitors or use of *Treximet* within 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated.[26] MAO-A inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. In patients taking MAO-A inhibitors, sumatriptan plasma levels attained after treatment with recommended doses are 7-fold higher following oral administration than those obtained under other conditions.

Concomitant Use with Serotonin Selective Reuptake Inhibitors (SSRIs)

The development of a potentially life-threatening serotonin syndrome may occur with triptans, including treatment with *Treximet*, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).[26] If concomitant treatment with *Treximet* and an SSRI (e.g., fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram) or SNRI (e.g., venlafaxine, duloxetine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Cases of life-threatening serotonin syndrome have been reported during combined use of SSRIs or SNRIs and triptans.[26]

Since *Treximet* contains sumatriptan, it should not be administered within 24 hours of another 5 HT_1 agonist.

Concomitant Use with Imitrex Injection

We are not aware of any completed studies or other data that specifically address this issue. GlaxoSmithKline is conducting a pharmacokinetic study evaluating the use of *Treximet* prior to or following administration of *Imitrex* Injection; results are not currently available.

Concomitant Use with Propranolol and Other Beta Blockers

Propranolol, a representative agent of the beta-blocker class, was investigated for potential drug interaction with sumatriptan. [26,87] Results of a double-blind, randomized, crossover study showed no statistically significant effects of a single oral dose of sumatriptan (300 mg) on pharmacokinetic variables [maximum plasma concentration (Cmax), time to maximum plasma concentration (tmax), AUC, and half-life (t½)] after 7 days of dosing with propranolol (80 mg twice daily) in 10 healthy male volunteers.

Naproxen and other non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the antihypertensive effect of propranolol and other beta-blockers.[26]

Concomitant Use with Other Triptans

Since *Treximet* contains sumatriptan, it should not be administered within 24 hours of another 5-HT_1 agonist. [26] It is a contraindication to administer *Treximet* with another triptan-containing medication.

Concomitant Use with Ergotamine-Containing Medications

Treximet and any ergotamine-containing or ergot-type medication (like dihydroergotamine or methysergide) should not be used within 24 hours of each other.[26]

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (e.g., dihydroergotamine, methysergide) and *Treximet* within 24 hours of each other should be avoided.

Concomitant Use with Aspirin

When naproxen is administered with aspirin, its protein binding is reduced, although the clearance of free naproxen is not altered.[26] The clinical significance of this interaction is not known; however, as with other non-steroidal anti-inflammatory (NSAID)-containing products, concomitant administration of *Treximet* and aspirin is not generally recommended because of the potential of increased adverse effects.

Anaphylactic/Anaphylactoid Reactions

As with other nonsteroidal antiinflammatory-containing products, anaphylactic/anaphylactoid reactions may occur in patients without known prior exposure to naproxen. *Treximet* should not be given to patients with the aspirin triad. This symptom complex typically occurs in patients with asthma who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal brochospasm after taking aspirin or other NSAIDs.

Treximet is contraindicated in patients in whom aspirin or other nonsteroidal anti-inflammatory/analgesic drugs induce the syndrome of asthma, rhinitis, and nasal polyps. Anaphylactic/anaphylactoid reactions to naproxen, whether of the true allergic type or the pharmacologic idiosyncratic type (e.g., aspirin hypersensitivity syndrome), usually but not always occur in patients with a known history of such reactions. Both types of reactions have the potential of being fatal. Therefore, careful questioning of patients for medical conditions such as asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs before starting therapy is important. In addition, if such symptoms occur during therapy, treatment should be discontinued.

Pre-existing Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm that can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, *Treximet* should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Cardiac and Gastrointestinal Events

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious gastrointestinal events.

Concomitant Use with Warfarin

The effects of warfarin and non-steroidal anti-inflammatory drugs (NSAIDs) on gastrointestinal (GI) bleeding are synergistic, such that patients taking both drugs have a higher risk of serious GI bleeding than patients taking either drug alone.(26)

Concomitant Use with Angiotensin-Converting Enzyme (ACE) Inhibitors

Reports suggest that non-steroidal anti-inflammatory drugs (NSAIDs) may diminish the antihypertensive effect of angiotensin-converting enzyme (ACE) inhibitors.(26) The use of *Treximet* in patients who are receiving ACE inhibitors may potentiate renal disease states.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.(26) Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

4.14 Dosing and Administration

Dosing and Administration

Treximet is a fixed combination containing doses of sumatriptan (85 mg) and naproxen sodium (500 mg) within the approved dosage ranges of the individual components (25 to 100 mg of sumatriptan and 220 to 825 mg of naproxen sodium). *Treximet* contains a dose of sumatriptan higher than the lowest effective dose. Individuals may vary in response to doses of sumatriptan. The choice of the dose of sumatriptan, and of the use of a fixed dose combination such as in *Treximet* should therefore be made on an individual basis, weighing the possible benefit of a higher dose of sumatriptan with the potential for a greater risk of adverse events. Carefully consider the potential benefits and risks of *Treximet* and other treatment options when deciding to use *Treximet*. The recommended dose is 1 tablet. In controlled clinical trials, single doses of *Treximet* were effective for the acute treatment of migraine in adults.

Second Dose of Treximet

The efficacy of taking a second dose has not been established. Do not take more than 2 *Treximet* tablets in 24 hours. Dosing of tablets should be at least 2 hours apart. The safety of treating an average of more than 5 migraine headaches in a 30 day period has not been established.

4.15 Co-prescribed/Concomitant Therapies

Refer to Enclosed Prescribing Information.

5. EFFICACY AND SAFETY TRIALS (FDA APPROVED INDICATIONS)

5.1 Overview of *Treximet* Clinical Program

Over 3,500 patients treated approximately 30,000 migraine attacks to date in the *Treximet* clinical program.(14)

The *Treximet* clinical program is comprised of ten randomized, double-blind, placebo-controlled, multi-center studies. Two of these studies included patients who treated their migraines during moderate or severe pain.(24) These pivotal single-attack studies, compared the efficacy and safety of *Treximet* to placebo as well as to each individual component of the combination tablet. The remaining eight studies followed an early intervention paradigm, in which patients treated with either *Treximet* or placebo during the mild pain phase and within one hour of pain onset.(8,9,17,18,19,20,21,22) Pairs of identical studies were performed to assess the efficacy of *Treximet* in early intervention, in consistency across attacks and within individual patients, in patients with menstrually-related migraine and dysmenorrhea, and in patients who did not previously respond to or tolerate another short-acting triptan. The clinical program assessed the efficacy of *Treximet* for migraine across multiple patient populations, and with robust study designs including early, sustained, and composite endpoints.

In addition, a 12 month, open-label, multi-attack, repeat dose study examined the safety of single doses of *Treximet* in the acute treatment of migraine.[23] Patients in this study treated during moderate or severe pain, with an optional second dose. Finally, six cross-over studies defined the pharmacokinetic profile of *Treximet*.[12,80,81,82,83,88]

5.2 Efficacy of *Treximet* at Early Timepoints

2 and 4 Hour Pain Relief

In clinical studies for *Treximet*, pain relief was defined as percentage of patients with a reduction from moderate or severe pain to mild or no pain. These endpoints were evaluated in two randomized, double-blind, parallel group single-attack studies, in which patients treated during moderate or severe pain.[24] In these studies, patients were randomized to receive *Treximet*, sumatriptan 85 mg, naproxen sodium 500 mg, or placebo. In these studies, *Treximet* was superior to sumatriptan 85 mg for 2 and 4 hour pain relief. Results are shown in Table 2.

Table 2. Two and Four Hour Pain Relief with *Treximet* (Intent to Treat Population)[24]

Study Number	**MT400-301**				**MT400-302**			
Treatment Arms	*Treximet* (n=364)	Sumatriptan 85 mg (n=361)	Naproxen 500 mg (n=356)	Placebo (n=360)	*Treximet* (n=362)	Sumatriptan 85 mg (n=362)	Naproxen 500 mg (n=364)	Placebo (n=382)
Pain relief 2 hours (%)	57*†	50	43	29	65*†	55	44	28
Pain relief 4 hours (%)	72*†	61	54	37	78*†	66	55	37
*$P<0.001$ vs. placebo; †$P<0.05$ vs. sumatriptan 85 mg								

2 and 4 Hour Pain-Free

In clinical studies for *Treximet*, 2 and 4 hour pain-free endpoints were evaluated in eight randomized, double-blind, placebo-controlled studies. In two of these studies, patients were randomized to receive *Treximet*, sumatriptan 85 mg, naproxen sodium 500 mg, or placebo and treated during moderate or severe pain. Pain-free was defined as the percentage of patients with a reduction from moderate or severe pain to no pain. In these studies evaluating *Treximet* in a moderate-to-severe paradigm, *Treximet* provided superior pain-free results at 2 and 4 hours compared to the active comparator sumatriptan 85 mg.[24] In the remaining studies, patients were randomized to receive *Treximet* or placebo and treated during the mild pain phase and within one hour of pain onset.[8,9,17,18,19,20,21,22] In these early intervention studies, pain-free was defined as the percentage of patients with a reduction from mild pain to no pain. In all of these studies, *Treximet* provided superior pain-free results compared to placebo. Results are shown in Table 3.

Table 3. Two and Four Hour Pain-Free with *Treximet* (Intent to Treat Populations)

Treatment Paradigm	**Study Number**	**Treatment Arms**	**2 Hour Pain-Free (%)**	**4 Hour Pain-Free (%)**
Moderate-Severe	MT400-301[24]	*Treximet* (n=364)	30*†§	50*†§
		Sumatriptan 85 mg (n=361)	23	41
		Naproxen 500 mg (n=356)	16	26
		Placebo (n=360)	10	14
	MT400-302[24]	*Treximet* (n=362)	34*†§	56*†§
		Sumatriptan 85 mg (n=362)	25	42
		Naproxen 500 mg (n=364)	15	27
*$P<0.001$ vs. placebo; †$P<0.05$ vs. sumatriptan 85 mg; ‡ across attack comparisons made using repeated measures analysis; § post-hoc analysis; OR=Odds Ratio; CI=95% confidence interval for odds ratio				

Treatment Paradigm	Study Number	Treatment Arms	2 Hour Pain-Free (%)	4 Hour Pain-Free (%)
		Placebo (n=382)	9	16
Early Intervention	101998[17]	*Treximet* (n=280)	52*	70*
		Placebo (n=296)	17	25
	101999[18]	*Treximet* (n=276)	51*	67*
		Placebo (n=259)	15	25
Early Intervention. Four period, cross-over, multi-attack consistency study. Patients randomized to one of five treatment sequences.	103632‡[19]	*Treximet* (n=1665)	52*	75*
		Placebo (n=422)	25	38
	103635‡[20]	*Treximet* (n=1655)	50*	72*
		Placebo (n=416)	20	33
Early Intervention. Patients included with pure menstrual migraine or menstrually-related migraine and dysmenorrhea at onset of menstruation.	105850[21]	*Treximet* (n=151)	42*	60*
		Placebo (n=160)	23	36
	105852[22]	*Treximet* (n=151)	52*	66*
		Placebo (n=159)	22	30
Early Intervention. Patients included if they reported having discontinued treatment with a short-acting triptan (rizatriptan, sumatriptan, almotriptan, zolmitriptan, and eletriptan) within a year due to non-response, poor response, or intolerance.	106571[9]	*Treximet* (n=136) [OR (CI)]	40% [3.19 (1.80, 5.65)]*	59% [4.93 (2.85, 8.54)]*
		Placebo (n=134) [OR (CI)]	17%	23%
	106573[8]	*Treximet* (n=134) [OR (CI)]	44% [4.69 (2.57, 8.55)]*	62% [8.11 (4.37 , 15.03)]*
		Placebo (n=133) [OR (CI)]	14%	17%

*$P<0.001$ vs. placebo; †$P<0.05$ vs. sumatriptan 85 mg; ‡ across attack comparisons made using repeated measures analysis; § post-hoc analysis; OR=Odds Ratio; CI=95% confidence interval for odds ratio

2 and 4 Hour Migraine-Free

Migraine-free is considered the most difficult endpoint to achieve, because patients are required to be pain-free with no associated symptoms (photophobia, phonophobia, nausea/vomiting). In clinical studies for *Treximet*, migraine-free was defined as percent of subjects with moderate or severe pain at baseline who had no pain and lacked all associated symptoms (photophobia, phonophobia, nausea/vomiting) at endpoint. Migraine-free was evaluated post-hoc in two studies evaluating patients who were randomized to receive *Treximet*, sumatriptan 85 mg, naproxen sodium 500 mg, or placebo and who treated during moderate or severe pain.[24] In 8 additional studies, patients were randomized to receive *Treximet* or placebo and treated during the mild pain phase and within one hour of pain onset.[8,9,17,18,19,20,21,22]

Treximet was superior to placebo for migraine-free at 2 and 4 hours across all of the studies. In addition, *Treximet* was superior to sumatriptan 85 mg at 4 hours in patients treating moderate-to-severe pain. Results are shown in Table 4.

Table 4. Two and Four Hour Migraine-Free with *Treximet* (Intent to Treat Populations)

Treatment Paradigm	Study Number	Treatment Arms	2 Hour Migraine-Free (%)	4 Hour Migraine-Free (%)
Moderate-Severe (Post-hoc analysis not adjusted for multiple endpoints)	MT400-301[24]	*Treximet* (n=364)	23*	45*†
		Sumatriptan 85 mg (n=361)	19	38
		Naproxen 500 mg (n=356)	14	24
		Placebo (n=360)	9	13
	MT400-302[24]	*Treximet* (n=362)	29*	51*†
		Sumatriptan 85 mg (n=362)	22	37
		Naproxen 500 mg (n=364)	13	25
		Placebo (n=382)	9	15
Early Intervention.	101998[17]	*Treximet* (n=280)	45*	63*
		Placebo (n=296)	15	24
	101999[18]	*Treximet* (n=276)	46*	64*
		Placebo (n=259)	14	25
Early Intervention. Four period, cross-over, multi-attack consistency study. Patients randomized to one of five treatment sequences.	103632§[19]	*Treximet* (n=1665)	44*	69*
		Placebo (n=422)	21	36
	103635§[20]	*Treximet* (n=1655)	43*	66*
		Placebo (n=416)	17	31
Early Intervention. Patients included with pure menstrual migraine or menstrually-related migraine and dysmenorrhea at onset of menstruation.	105850[21]	*Treximet* (n=151)	33‖	55‖
		Placebo (n=160)	19	29
	105852[22]	*Treximet* (n=151)	44‖	60‖
		Placebo (n=159)	19	27

*$P<0.001$ vs. placebo; †$P<0.05$ vs. sumatriptan 85 mg; ‡$P<0.05$ vs. placebo; § across attack comparisons made using repeated measures analysis; ‖unadjusted p value $P<0.05$ (comparison not adjusted for multiplicity); OR=Odds Ratio; CI=95% confidence interval for odds ratio

Treatment Paradigm	Study Number	Treatment Arms	2 Hour Migraine-Free (%)	4 Hour Migraine-Free (%)
Early Intervention. Patients included if they reported having discontinued treatment with a short-acting triptan (rizatriptan, sumatriptan, almotriptan, zolmitriptan, and eletriptan) within a year due to non-response, poor response, or intolerance.	106571[9]	*Treximet* (n=136) [OR (CI)]	35% [3.18 (1.75, 5.76)]*	53% [3.88 (2.27, 6.61)]*
		Placebo (n=134) [OR (CI)]	14%	23%
	106573[8]	*Treximet* (n=134) [OR (CI)]	35% [4.14 (2.20, 7.80)]*	57% [7.85 (4.17, 14.77)]*
		Placebo (n=133) [OR (CI)]	11%	15%

*$P<0.001$ vs. placebo; †$P<0.05$ vs. sumatriptan 85 mg; ‡$P<0.05$ vs. placebo; § across attack comparisons made using repeated measures analysis; ‖unadjusted p value $P<0.05$ (comparison not adjusted for multiplicity); OR=Odds Ratio; CI=95% confidence interval for odds ratio

5.3 Sustained Efficacy of *Treximet*

Sustained Pain Relief

In clinical studies for *Treximet*, sustained pain relief was defined as the percentage of patients who achieved a reduction from moderate to severe pain at treatment to mild or no pain from 2 hours through 24 hours after dosing, with no use of rescue medication. This endpoint was evaluated in two randomized, double-blind, parallel group single-attack studies, in which patients treated during moderate or severe pain.[24] In these studies, patients were randomized to receive *Treximet*, sumatriptan 85 mg, naproxen sodium 500 mg, or placebo. In both studies, *Treximet* was superior to sumatriptan 85 mg for sustained pain relief. Results are shown in Table 5.

Table 5. Sustained Pain Relief (2-24 hours) with *Treximet* (Intent to Treat Population)[24]

Study Number	**MT400-301**				**MT400-302**			
Treatment Arms	*Treximet* (n=364)	Sumatriptan 85 mg (n=361)	Naproxen 500 mg (n=356)	Placebo (n=360)	*Treximet* (n=362)	Sumatriptan 85 mg (n=362)	Naproxen 500 mg (n=364)	Placebo (n=382)
2-24 hour Sustained Pain Relief (%)	44*†	33	28	17	48*†	35	30	18

*$P<0.001$ vs. placebo; †$P<0.05$ vs. sumatriptan 85 mg

Sustained Pain-Free

In clinical studies for *Treximet*, sustained pain-freedom was evaluated in 10 randomized, double-blind, placebo-controlled studies. In two of these studies, patients were randomized to receive *Treximet*, sumatriptan 85 mg, naproxen sodium 500 mg, or placebo and treated during moderate or severe pain. Sustained pain-free was defined as the percentage of patients who achieved a reduction from moderate to severe pain to no pain at 2 hours and maintained no pain until 24 hours with no use of rescue medication. In these studies evaluating *Treximet* in a moderate-to-severe paradigm, *Treximet* provided superior sustained pain-free results compared to the active comparator sumatriptan 85 mg.[24] In the remaining studies, patients were randomized to receive *Treximet* or placebo and treated during the mild pain phase and within one hour of pain onset.[8,9,17,18,19,20,21,22] In these studies, sustained pain-free was defined as the percentage of patients who achieved a reduction from mild pain to no pain at 2 hours and maintained no

pain until 24 hours with no use of rescue medication.. In all of these studies, *Treximet* provided superior pain-free results compared to placebo. Results are shown in Table 6.

Table 6. Sustained Pain-Free (2-24 hours) with *Treximet* (Intent to Treat Populations)

Treatment Paradigm	Study Number	Treatment Arms	2-24 hour Sustained Pain Free (%)
Moderate-Severe	MT400-301[24]	*Treximet* (n=364)	23*†
		Sumatriptan 85 mg (n=361)	14
		Naproxen 500 mg (n=356)	10
		Placebo (n=360)	7
	MT400-302[24]	*Treximet* (n=362)	25*†
		Sumatriptan 85 mg (n=362)	16
		Naproxen 500 mg (n=364)	10
		Placebo (n=382)	8
Early Intervention	101998[17]	*Treximet* (n=280)	45*
		Placebo (n=296)	12
	101999[18]	*Treximet* (n=276)	40*
		Placebo (n=259)	14
Early Intervention. Four period, cross-over, multi-attack consistency study. Patients randomized to one of five treatment sequences.	103632§[19]	*Treximet* (n=1665)	37*
		Placebo (n=422)	17
	103635§[20]	*Treximet* (n=1656)	34*
		Placebo (n=416)	12
Early Intervention. Patients included with pure menstrual migraine or menstrually-related migraine and dysmenorrhea at onset of menstruation.	105850[21]	*Treximet* (n=151)	29‡
		Placebo (n=160)	18
	105852[22]	*Treximet* (n=151)	38*
		Placebo (n=159)	10
Early Intervention. Patients included if they reported having discontinued treatment with a short-acting triptan (rizatriptan, sumatriptan, almotriptan, zolmitriptan, and eletriptan) within a year due to non-response, poor response, or intolerance.	106571[9]	*Treximet* (n=136) [OR (CI)]	26% [4.50 (2.17, 9.36)]*
		Placebo (n=134) [OR (CI)]	8%
	106573[8]	*Treximet* (n=134) [OR (CI)]	31% [5.63 (2.76, 11.49)]*
		Placebo (n=133) [OR (CI)]	8%

*P<0.001 vs. placebo; †P<0.05 vs. sumatriptan 85 mg; ‡P<0.05 vs. placebo; § across attack comparisons made using repeated measures analysis; OR=Odds Ratio; CI=95% confidence interval for odds ratio

Rescue

In clinical studies for *Treximet*, rescue was evaluated in eight randomized, double-blind, placebo-controlled studies. Rescue was defined as the percentage of patients who used additional medication to treat their migraine through 24 hours after dosing. In these studies, patients were permitted to take rescue medication beginning 2 hours after dosing, with the exception of ergot-containing medications, serotonin agonists, or NSAID-containing products (except Studies 106571 and 106573; patients could rescue with naproxen). In two of these studies, patients were randomized to receive *Treximet*, sumatriptan 85 mg, naproxen

sodium 500 mg, or placebo and treated during moderate or severe pain. In these studies evaluating *Treximet* in a moderate-to-severe paradigm, significantly less patients who took *Treximet* used rescue medication, compared to the active comparator sumatriptan 85 mg.[24] In 6 additional studies, patients were randomized to receive *Treximet* or placebo and treated during the mild pain phase and within one hour of pain onset.[8,9,17,18,19,20,21,22] Treximet was superior to placebo for rescue across all of the early intervention studies. Results are shown in Table 7.

Table 7. Patients Requiring Rescue Medication (Intent to Treat Populations)

Treatment Paradigm	Study Number	Treatment Arms	Rescue (%)
Moderate-Severe	MT400-301[24]	*Treximet* (n=364)	23*†§
		Sumatriptan 85 mg (n=361)	38
		Naproxen 500 mg (n=356)	39
		Placebo (n=360)	58
	MT400-302[24]	*Treximet* (n=362)	22*†§
		Sumatriptan 85 mg (n=362)	32
		Naproxen 500 mg (n=364)	38
		Placebo (n=259)	53
Early Intervention	101998[17]	*Treximet* (n=280)	20*
		Placebo (n=296)	47
	101999[18]	*Treximet* (n=276)	16*
		Placebo (n=259)	45
Early Intervention. Patients included with pure menstrual migraine or menstrually-related migraine and dysmenorrhea at onset of menstruation. Patients permitted to take second dose of study medication beginning at two hours after first dose.	105850[21]	*Treximet* (n=151)	36‡
		Placebo (n=160)	53
	105852[22]	*Treximet* (n=151)	30*
		Placebo (n=159)	67
Early Intervention. Patients included if they reported having discontinued treatment with a short-acting triptan (rizatriptan, sumatriptan, almotriptan, zolmitriptan, and eletriptan) within a year due to non-response, poor response, or intolerance.	106571[9]	*Treximet* (n=136) [OR (CI)]	29% [0.24 (0.16, 0.38)]*
		Placebo (n=134) [OR (CI)]	63%
	106573[8]	*Treximet* (n=134) [OR (CI)]	22% [0.22 (0.14, 0.37)]*
		Placebo (n=133) [OR (CI)]	55%

*P<0.001 vs. placebo; †P<0.05 vs. sumatriptan 85 mg; ‡ P<0.05 vs. placebo; § post-hoc analysis; OR=Odds Ratio; CI=95% confidence interval for odds ratio

5.4 *Treximet* Provided Consistent Relief Across Four Attacks

The consistency of response for *Treximet* when treating migraine at the mild pain phase was evaluated in two identical randomized, double-blind, multi-center, placebo-controlled, 4-period crossover, multi-attack studies.[19,20] In these studies, patients were randomized to one of five treatment sequences that included *Treximet* and placebo, and were instructed to treat up to four eligible migraine attacks over a 4-month

period. In the repeated measures analysis, across all attacks taken together, *Treximet* provided superior and consistent 2 and 4 hour pain-freedom, 2 and 4 hour migraine-freedom, sustained pain-freedom from 2-24 hours, and lower use of rescue medication compared to placebo. These data demonstrate that the efficacy of *Treximet* is maintained across attacks in a population of migraineurs.

5.5 *Treximet* Provided Consistent Relief Within Individual Patients Across Four Attacks

The consistency of response for *Treximet* when treating migraine at the mild pain phase was evaluated in two identical randomized, double-blind, multi-center, placebo-controlled, 4-period crossover, multi-attack studies.[19,20] In these studies, patients were randomized to one of five treatment sequences that included *Treximet* and placebo, and were instructed to treat up to four eligible migraine attacks over a 4-month period. These studies demonstrated within-patient consistency for 2 and 4 hour pain-free and sustained pain free from 2-24 hours. Additionally, these studies demonstrated consistency from the first to the second attack treated with *Treximet* for 2 and 4 hour pain-free and sustained pain-free from 2-24 hours. These data demonstrate that the efficacy of *Treximet* is consistently maintained within an individual patient across multiple attacks.

5.6 Efficacy of *Treximet* in Patients who Responded Poorly or Did Not Tolerate Other Short-Acting Triptans

The efficacy of *Treximet* when treating migraine in patients who had previously discontinued treatment with a short-acting triptan due to poor response or intolerance were evaluated in two identical randomized, double-blind, placebo-controlled, cross-over, early intervention, two-attack studies.[8,9] Eligible patients had recently (within 1 year) discontinued treatment with a short-acting triptan (rizatriptan, sumatriptan, almotriptan, zolmitriptan, and eletriptan) due to poor response or intolerance, representing a difficult-to-treat patient population. Poor response was defined as patient-reported discontinuation of treatment with any of the aforementioned triptans for reasons related to response, including (but not limited to): slow onset of efficacy, inconsistent efficacy, inadequate overall efficacy, or inadequate sustained efficacy through 24 hours. Intolerance was defined as patient reported discontinuation of treatment with a short-acting triptan for other reasons, attributable to the triptan, outside of poor response. Patients were instructed to treat two separate migraine attacks during the mild phase of each attack and within one hour of the onset of headache pain. One attack was treated with one tablet of *Treximet* and the other attack with one tablet of placebo (crossover design; randomized treatment order). Rescue medication was permitted at 2 hours post-dose which may have been a single dose of sumatriptan, naproxen, an over-the-counter (OTC) pain-reliever, or an antiemetic.

In these studies, *Treximet* provided superior 2 and 4 hour pain-freedom, 2 and 4 hour migraine-freedom, sustained pain-freedom from 2-24 hours, and significantly lower use of rescue medication.[8,9] I

5.7 Efficacy of *Treximet* in Patients with Menstrually-Related Migraine

The efficacy of *Treximet* when treating menstrual migraine at the mild pain phase was evaluated in two identical randomized, double blind, placebo-controlled, parallel group, single attack studies.[21,22] Eligible women were classified as meeting either pure menstrual migraine or menstrually-related migraine criteria. Additionally, this study was uniquely designed to include only women who had experienced dysmenorrhea (menstrual pain) at the onset of menstruation in at least two of three months prior to screening. Thus, the subjects in these studies had a history of two pain conditions. Rescue medication was allowed beginning at 2 hours post-dose which may have been a second dose of *Treximet*. In these studies, Treximet provided superior 2 and 4 hour pain-freedom, 2 and 4 hour migraine-freedom, sustained pain-freedom from 2-24 hours, and demonstrated lower use of total rescue medication, and lower rescue for headache and for menstrual symptoms, compared to placebo. In addition, *Treximet* provided superior results over placebo for several endpoints that evaluated menstrual symptoms including: relief of a composite endpoint of bloating, tiredness and irritability at 1 (Study 105850 only), 2, and 4 hours; relief of irritability at 1, 2, and 4 hours; and relief of tiredness at 2 (Study 105850 only) hours and 4 (Study 105850 only) hours. Additionally, *Treximet* demonstrated superior relief of a composite endpoint of abdominal and back pain at 4 hours, relief of abdominal pain at 2 (Study 105850 only) hours and 4 hours, and relief of back pain at 4 hours (Study 105852 only), although these results were not adjusted for multiple comparisons.

5.8 Adverse Effects of *Treximet*

Safety of Treximet for Acute Treatment of Migraine in Moderate or Severe Pain

Table 8 lists adverse events that occurred in two placebo-controlled clinical trials in evaluating patients who took at least one dose of study drug and treated their migraines during moderate or severe pain.

Table 8. Treatment Emergent Adverse Events Reported by at Least 2% of Patients in Two Controlled Trials in Moderate to Severe Migraine*[24]

	Percent of Patients Reporting			
Adverse Event	***Treximet*** **(n=737)**	**Placebo (n=752)**	**Sumatriptan 85 mg (n=735)**	**Naproxen sodium 500 mg (n=732)**
Nervous System Disorders				
Dizziness	4	2	2	2
Somnolence	3	2	2	2
Paresthesia	2	<1	2	<1
Gastrointestinal Disorders				
Nausea	3	1	3	<1
Dyspepsia	2	1	2	1
Dry mouth	2	1	2	<1
Pain and other pressure sensations				
Chest discomfort/ chest pain	3	<1	2	1
Neck/throat/jaw pain/tightness/ pressure	3	1	3	1
*Events that occurred at a frequency of 2% or more in the group treated with *Treximet* and that occurred more frequently in the group treated with *Treximet* that in the placebo group				

Other events that occurred in more than 1% of patients receiving *Treximet* and occurred at a greater frequency than the placebo group included asthenia, feeling hot, muscle tightness, and palpitations.

Long-Term Safety of Treximet

Table 9 lists adverse events that occurred in a 12-month, open-label, multicenter, multiple attack, repeat dose study examining the safety of single doses of *Treximet*.[23] Patients treated with *Treximet* during moderate or severe pain, with an optional second dose to treat the same attack at least two hours after the first dose. Other rescue medications (excluding NSAIDs, ergots, and other 5-HT_1 agonists) were permitted after taking the last dose of study medication. The complete study population consisted of 565 patients, with a total of 414 patients completing six months (treating at least 12 attacks), and 362 completing 12 months of the study (treating at least 24 attacks).

In the overall safety population (n=565), 24,485 attacks were treated with *Treximet*. Of those attacks, 17,144 or 70% were treated with just one dose of study medication.

Table 9. Treatment Emergent Adverse Events Reported in ≥ 2% of Patients (n = 565)[23]

	Related n (%)
Nausea	34 (6%)
Dyspepsia	14 (2%)
Dizziness	18 (3%)
Upper Abdominal Pain	9 (2%)
Muscle tightness	19 (3%)
Paresthesia	12 (2%)
Chest Discomfort	10 (2%)

Of the patients withdrawn from the study due to adverse events, two patients discontinued due to pregnancy, five due to serious adverse events, and 36 due to adverse events.[23] Fourteen patients (2%) experienced one or more serious adverse events, with no specific pattern identified. Only one was judged

to be probably related to study drug. A diagnosis of acute coronary syndrome was made in a 47 year-old female. She was found to have significant single-vessel coronary artery disease on angiography. The patient had the following risk factors for coronary artery disease: obesity (body mass index 35.7), a family history of cardiovascular disease, and hypercholesteremia. She had used sumatriptan tablets prior to entry into the study. About two hours after one dose, she experienced chest discomfort and shortness of breath. Prior to this event, she had been enrolled in the study for approximately seven months and had treated multiple migraine attacks with study drug.

Safety of Treximet in Other Clinical Studies

For the remaining clinical studies, please refer to Table 10 in the Appendix to see all adverse events that occurred at a frequency of at least 2% in the *Treximet* group.

5.9 *Treximet* Evidence Table

Table 10. - See Appendix

6. OTHER STUDIED USES

6.1 Use of *Treximet* for Neck Pain During a Migraine Attack

Please refer to Table 10 in the Appendix for study design details and an overview of the safety data for the studies discussed in this section.

Treatment of Mild Migraine Pain: Presence of Neck Pain/Discomfort

The presence or absence of neck pain/discomfort was recorded in patient diaries immediately before taking study medication and at two and four hours post dose. *Treximet* significantly reduced the incidence of neck pain/discomfort compared to placebo (Table 11).

Table 11. Presence of Neck Pain/Discomfort Symptoms Associated with Migraine at Baseline, 2, and 4 Hours Post-dose[17,18]

	Study 101998		Study 101999	
	***Treximet* (n = 280)**	**Placebo (n = 296)**	***Treximet* (n = 276)**	**Placebo (n = 259)**
Baseline	63%	58%	63%	63%
2 Hours	35%*	44%	28% †	54%
4 Hours	19% †	38%	19% †	46%
*$P = 0.001$ vs. placebo †$P < 0.001$ vs placebo				

Consistency of Response Studies: Percent of Attacks with Neck Pain/Discomfort

The presence or absence of neck pain/discomfort was recorded in patient diaries immediately before taking study medication and at specified intervals up to six hours post-dose. In the repeated measures analysis, *Treximet* significantly reduced the incidence of neck pain/discomfort at two, four, and six hours post-dose across all attacks compared to placebo (Table 12).[19,20]

Table 12. Percent of Attacks with Neck Pain/Discomfort (Using Repeated Measures Analysis)[19,20]

	Study 1		Study 2	
	***Treximet* (n=1645)**	**Placebo (n=416)**	***Treximet* (n=1640)**	**Placebo (n=409)**
Baseline	59%	61%	59%	59%
2 Hours	32%*	42%	35%*	46%
4 Hours	18%*	35%	20%*	38%
6 Hours	15%*	30%	15%*	34%
*$P < 0.001$ vs. placebo				

Treatment of Menstrual Migraine: Incidence of Neck Pain/Discomfort

In these studies, the incidence of neck pain/discomfort was evaluated at 2 and 4 hours after dosing with placebo or *Treximet*.[21,22] Additionally, the incidence of sustained neck pain/discomfort freedom was evaluated from 4-24 hours after dosing (see Table 13). These comparisons were not adjusted for multiplicity.

Table 13. Incidence of Neck Pain/Discomfort Associated with Migraine and Sustained (4-24 hour) Freedom from Neck Pain/Discomfort Post-Dose [21,22]

	Study105850		Study 10582	
	Treximet (n=151)	Placebo (n=160)	*Treximet* (n=151)	Placebo (n=159)
Baseline	62%	65%	70%	57%
2 Hours	40%	49%	33%*	42%
4 Hours	28%	34%	23%*	29%
Sustained Neck Pain/Discomfort Freedom (4-24 Hours)	24%	18%	20%	14%
*unadjusted p value $P<0.05$ (comparison not controlled for multiplicity)				

Treatment of migraine in patients who report poor response to previous short-acting triptan use: Incidence of neck pain

In these studies, the incidence of neck pain was evaluated at 2, 4, and 8 hours after dosing with placebo or *Treximet*.[8,9] Additionally, the incidence of sustained neck pain freedom was evaluated from 2-24 hours after dosing (see Table 14). Unlike the other studies included in this response, the neck pain endpoint did not include discomfort.

Table 14. Incidence of Neck Pain Associated with Migraine and Sustained (2-24 hour) Freedom from Neck Pain Post-Dose[8,9]

	Study 106571		Study 106573	
	Treximet (n=136)	Placebo (n=134)	*Treximet* (n=134)	Placebo (n=133)
Baseline	60%	49%	57%	63%
2 Hours [OR (CI)]	40% [0.94 (0.64, 1.37)]	41%	39% [(0.54 (0.37, 0.79)]†	55%
4 Hours [OR (CI)]	29% [(0.76 (0.51, 1.15)]	35%	29% [0.40 (0.26, 0.61)]*	50%
8 Hours [OR (CI)]	23% [0.72 (0.48, 1.08)]	28%	22% [0.42 (0.27, 0.67)]*	39%
Sustained Neck Pain Freedom (2-24 Hours) [OR (CI)]	46% [2.67 (1.70, 4.21)]*	25%	49% [3.38 (2.12, 5.39)]*	22%
OR=odds ratio; CI=95% confidence interval for odds ratio; * $P<0.001$ vs placebo; † $P=0.002$				

6.2 Use of *Treximet* for Relief of Sinus Symptoms During a Migraine Attack

Please refer to Table 10 in the Appendix for study design details and an overview of the safety data for the studies discussed in this section.

Treatment of Mild Migraine Pain: Incidence of Sinus Pain/PRessure

Treximet significantly reduced the incidence of sinus pain and pressure at two and four hours post-dose compared to placebo (Table 15).

Table 15. Presence of Sinus Pain/Pressure Associated with Migraine at Baseline, 2, and 4 Hours Post-dose[17,18]

	Study 101998		Study 101999	
	***Treximet* (N = 280)**	**Placebo (N = 296)**	***Treximet* (N = 276)**	**Placebo (N = 259)**
Baseline	43%	42%	52%	46%
* $P < 0.001$				

	Study 101998		**Study 101999**	
	***Treximet* (N = 280)**	**Placebo (N = 296)**	***Treximet* (N = 276)**	**Placebo (N = 259)**
2 hours	19%*	33%	23%*	38%
4 hours	10%*	30%	15%*	32%
* $P < 0.001$				

Consistency of Response Studies: Percent of Attacks with Sinus Pain/Pressure

The presence or absence of sinus pain/pressure was recorded in patient diaries immediately before taking study medication and at specified intervals up to six hours post-dose. In the repeated measures analysis, *Treximet* significantly reduced the incidence of sinus pain/pressure at two, four, and six hours post-dose across all attacks compared to placebo (Table 16).[19,20]

Table 16. Percent of Attacks with Sinus Pain/Pressure (Using Repeated Measures Analysis)[19,20]

	Study 1		Study 2	
	Treximet (n=1648)	Placebo (n=417)	*Treximet* (n=1640)	Placebo (n=408)
Baseline	39%	43%	42%	44%
2 Hours	18%*	31%	19%*	34%
4 Hours	10%*	27%	10%*	26%
6 Hours	8%*	23%	8%*	24%
*$P < 0.001$ vs. placebo				

Treatment of Menstrual Migraine: Incidence of Sinus Pain/Pressure

In these studies, the incidence of sinus pain/pressure was evaluated at 2 and 4 hours after dosing with placebo or *Treximet*.[21,22]Additionally, the incidence of sustained sinus pain/pressure freedom was evaluated from 4-24 hours after dosing (see Table 17).

Table 17. Incidence of Sinus Pain/Pressure Associated with Migraine and Sustained (4-24 hour) Freedom from Sinus Pain/Pressure Post-Dose [21,22]

	Study 105850		**Study 10582**	
	Treximet (n=151)	Placebo (n=160)	*Treximet* (n=151)	Placebo (n=159)
Baseline	47%	41%	56%	52%
2 Hours	25% *	30%	23% *	40%
4 Hours	17%	19%	17% *	26%
Sustained Sinus Pain/Pressure Freedom (4-24 Hours)	35%	31%	32% *	18%
* unadjusted p value $P<0.05$ (comparison not controlled for multiplicity)				

treatment of migraine in patients who report poor response to previous short-acting triptan use: Incidence of sinus pain

In these studies, the incidence of sinus pain was evaluated at 2, 4, and 8 hours after dosing with placebo or *Treximet*.[8,9] Additionally, the incidence of sustained sinus pain freedom was evaluated from 2-24 hours after dosing (see Table 18). Unlike the other studies included in this response, the sinus pain endpoint did not include pressure.

Table 18. Incidence of Sinus Pain Associated with Migraine and Sustained (2-24 hour) Freedom from Sinus Pain Post-Dose [8,9]

	Study 106571		Study 106573	
	Treximet (n=136)	Placebo (n=134)	*Treximet* (n=134)	Placebo (n=133)
Baseline	46%	44%	42%	36%
2 Hours [OR (CI)]	23% [0.46 (0.29, 0.73)]*	39%	31% [1.01 (0.65, 1.58)]	31%
4 Hours [OR (CI)]	15% [0.41 (0.24, 0.72)]†	29%	20% [0.65 (0.40, 1.06)]	28%
8 Hours [OR (CI)]	14% [(0.45 (0.28, 0.73)]*	26%	15% [0.66 (0.36, 1.18)]	21%
Sustained Sinus Pain Freedom (2-24 Hours) [OR (CI)]	56% [3.71 (2.29, 6.02)]*	26%	56% [2.55 (1.64, 3.95)]*	33%
OR=odds ratio; CI=95% confidence interval for odds ratio; * $P<0.001$ vs placebo; † $P=0.002$				

7. COMPARATIVE DATA

7.1 Comparison of *Treximet* with Naproxen Sodium

Treatment of Moderate to Severe Migraine Pain: Study Description

Please refer to the previously described section on this topic

Treatment of Moderate-Severe Migraine Pain: Efficacy Compared with Naproxen

Efficacy results comparing *Treximet* with naproxen sodium from both studies are presented in Table 19 and Table 20.

Prospective statistical analysis for the comparison of *Treximet* with naproxen sodium was performed for sustained pain-free endpoint only; analysis performed post-hoc for some additional endpoints.

Table 19. Comparison of the Efficacy of *Treximet* and Naproxen Sodium [24] [16] [15] [89]

	Study 1			Study 2		
	Treximet **(n = 364)**	**Naproxen Sodium 500 mg (n = 356)**	**Placebo (n = 360)**	***Treximet*** **(n = 362)**	**Naproxen Sodium 500 mg (n = 364)**	**Placebo (n = 382)**
Two Hour Data						
Pain Relief	65%*†	44%*	28%	57%*†	43%*	29%
Pain Free	34%*†	15%	9%	30%*†	16%	10%
Nausea free	71%‡	70%	65%	65%	68%	64%
Photophobia free	58%*§	47%	36%	50%*§	41%	32%
Phonophobia free	61%*§	51%	38%	56%*§	44%	34%
Four Hour Data						
Pain Relief	78%*†	55%	37%	72%*†	54%	37%
Pain Free	56%*†	27%	16%	50%*†	26%	14%
Nausea free	81%*§	67%	55%	73%*	68%	56%
Photophobia free	74%*§	57%	38%	69%*§	51%	38%
Phonophobia free	75%*§	60%	41%	72%*§	53%	38%
Sustained Efficacy Measures (2-24 hrs post-dose)						
Sustained Pain Relief‡	48%*†	30%	18%	44%*†	28%	17%
Sustained Pain Free‡	25%*†	10%	8%	23%*†	10%	7%
Sustained nausea free	56%*	44%	33%	48%*	41%	28%
Sustained photophobia free	46%*	31%	21%	37%*	27%	16%
Sustained phonophobia free	49%*	36%	21%	41%*	29%	18%
Use of rescue med	22%*§	38%	53%	23%*§	39%	58%
Recurrence§	13%	16%	25%	13%	22%	31%

*$P < 0.001$ vs. placebo; †$P < 0.001$ vs. naproxen sodium (Prospective statistical analysis was performed for sustained pain free endpoint only; others performed post-hoc.); ‡ $P<0.01$ vs. placebo; §$P<0.05$ vs. naproxen sodium (Prospective statistical analysis was performed for sustained pain free endpoint only; others performed post-hoc.)

‡Sustained pain relief/pain free defined as pain relief/pain free at 2 hours and maintenance of response through 24 hours post dose

§Recurrence was defined as pain relief at two hours followed by a return of moderate/severe pain; statistical analysis not performed.

Adjustments were made for a baseline nausea imbalance in Study 1

Table 20. Pain Relief Rates at Two Hours By Baseline Migraine Severity[24]

	Treximet	**Naproxen Sodium 500mg**	**Placebo**
Study 1			
Moderate baseline pain	75%* (n = 227)	48% (n = 228)	32% (n = 227)
Severe baseline pain	49%* (n = 137)	38% (n = 128)	22% (n = 133)
Study 2			
*$P<0.001$ vs. placebo (Statistical comparison was not part of the original planned analyses. Analysis was performed post hoc without adjustments for multiple comparisons.)			

	Treximet	**Naproxen Sodium 500mg**	**Placebo**
Moderate baseline pain	66%* (n = 212)	52% (n = 212)	32% (n = 230)
Severe baseline pain	45%* (n = 150)	32% (n = 152)	23% (n = 152)
**P*<0.001 vs. placebo (Statistical comparison was not part of the original planned analyses. Analysis was performed post hoc without adjustments for multiple comparisons.)			

Study results in the Table above demonstrate *Treximet* was more effective than naproxen sodium 500 mg for measures of two to 24 hour sustained pain-free response. Additionally, more patients taking *Treximet* reported pain relief and pain-free results at two and four hours, 2-24 hour sustained pain-relief response, and 2-24 hour sustained freedom of photophobia, phonophobia, and nausea versus patients taking naproxen.

Data from the two studies were pooled and results were consistent with the individual studies.

7.2 Comparison of *Treximet* with Sumatriptan

Treatment of Moderate to Severe Migraine Pain: Study Description

Please refer to the previously described section on this topic

Treatment of Moderate-Severe Migraine Pain: Efficacy Compared with Sumatriptan

Efficacy results comparing *Treximet* with sumatriptan from both studies are presented in Table 21 and Table 22.

Table 21. Comparison of the Efficacy of *Treximet* and Sumatriptan[15,16,24]

	Study 1			**Study 2**		
	Treximet **(n = 364)**	**Suma 85 mg (n = 361)**	**Placebo (n = 360)**	***Treximet*** **(n = 362)**	**Suma 85 mg (n = 362)**	**Placebo (n = 382)**
Two Hour Data						
Pain Relief	65%*†	55%	28%	57%*†	50%	29%
Pain Free	34%*§	25%	9%	30%*§	23%	10%
Nausea free	71%‡	66%	65%	65%	64%	64%
Photophobia free	58%*†	48%	36%	50%*	46%	32%
Phonophobia free	61%*†	50%	38%	56%*	52%	34%
Four Hour Data						
Pain Relief	78%*†	66%	37%	72%*†	61%	37%
Pain Free	56%*§	42%	16%	50%*§	41%	14%
Nausea free	81%*†	71%	55%	73%*	69%	56%
Photophobia free	74%*†	61%	38%	69%*†	59%	38%
Phonophobia free	75%*†	63%	41%	72%*†	62%	38%
Sustained Efficacy Measures (2-24 hrs post-dose)						
Sustained Pain Relief¶	48%*†	35%	18%	44%*†	33%	17%
Sustained Pain Free¶	25%*†	16%	8%	23%*†	14%	7%
Sustained nausea free	56%*†	44%	33%	48%*	44%	28%

**P* < 0.001 vs. placebo; †*P* < 0.05 vs. sumatriptan; ‡*P*<0.01 vs. placebo; §*P* < 0.05 vs. sumatriptan (Statistical comparison not part of original planned analysis; performed post-hoc without adjustments for multiple comparisons.); ||*P* = 0.05 vs. sumatriptan; #*P*<0.001 vs. placebo (Statistical comparison not part of original planned analysis; performed post-hoc without adjustments for multiple comparisons.)

¶Sustained pain relief/pain free defined as pain relief/pain free at 2 hours and maintenance of response through 24 hours post dose

**Recurrence defined as pain relief at two hours followed by a return of moderate/severe pain; statistical analysis not performed

Adjustments were made for a baseline nausea imbalance in Study 1

	Study 1			Study 2		
	Treximet **(n = 364)**	**Suma 85 mg (n = 361)**	**Placebo (n = 360)**	***Treximet*** **(n = 362)**	**Suma 85 mg (n = 362)**	**Placebo (n = 382)**
Sustained photophobia free	46%*†	35%	21%	37%*‖	30%	16%
Sustained phonophobia free	49%*†	36%	21%	41%*†	33%	18%
Use of rescue med	22%#†	32%	53%	23%#†	38%	58%
Recurrence**	13%	24%	25%	13%	19%	31%

*$P < 0.001$ vs. placebo; †$P < 0.05$ vs. sumatriptan; ‡$P<0.01$ vs. placebo; §$P < 0.05$ vs. sumatriptan (Statistical comparison not part of original planned analysis; performed post-hoc without adjustments for multiple comparisons.); ‖$P = 0.05$ vs. sumatriptan; #$P<0.001$ vs. placebo (Statistical comparison not part of original planned analysis; performed post-hoc without adjustments for multiple comparisons.)

¶Sustained pain relief/pain free defined as pain relief/pain free at 2 hours and maintenance of response through 24 hours post dose

**Recurrence defined as pain relief at two hours followed by a return of moderate/severe pain; statistical analysis not performed

Adjustments were made for a baseline nausea imbalance in Study 1

Table 22. Pain Relief Rates at Two Hours By Baseline Migraine Severity[24]

	Treximet	**Suma 85 mg**	**Placebo**
Study 1			
Moderate baseline pain	75%*† (n = 227)	64% (n = 232)	32% (n = 227)
Severe baseline pain	49%* (n = 137)	40% (n = 129)	22% (n = 133)
Study 2			
Moderate baseline pain	66%*§ (n = 212)	58% (n = 219)	32% (n = 230)
Severe baseline pain	45%* (n = 150)	38% (n = 143)	23% (n = 152)

Statistical comparison was not part of the original planned analyses. Analysis was performed post hoc without adjustments for multiple comparisons.

*$P < 0.001$ vs. placebo; †$P < 0.05$ vs. sumatriptan; §$P = 0.05$ vs. sumatriptan

Study results in the Table above demonstrate more patients achieved pain relief at two hours when treating moderate migraine versus severe migraine. In addition, more patients who treated with *Treximet* achieved pain relief at two hours compared with those who treated with sumatriptan regardless of migraine severity.

Data from the two studies were pooled and results were consistent with the individual studies.

8. OUTCOME AND ECONOMIC EVALUATION

8.1 Effect of *Treximet* on Quality of Life

Long-Term Safety Study: Description

An open-label, multicenter, multiple attack, repeat dose study examining the safety of single doses of *Treximet* in the acute treatment of migraine, with an optional second dose, was conducted over a 12 month period.[23] The study included adult outpatients, aged 18-65, with a demonstrated history (≥6 months) of migraine with or without aura according to the International Headache Society (IHS) criteria and were instructed to take one tablet of *Treximet* for each migraine attack of moderate or severe intensity. A second dose of *Treximet* could be used to treat the same migraine attack if at least two hours had elapsed after taking the first dose and additional treatment was deemed necessary by the patient due to inadequate relief. Other rescue medications (excluding NSAIDs, ergots and other 5-HT_1 agonists) were allowed 2 hours after taking the last dose of study medication. The complete study population consisted of 565 patients, with a total of 414 patients completing six months (treating at least 12 attacks), and 362 completed twelve months of the study (treating at least 24 attacks).

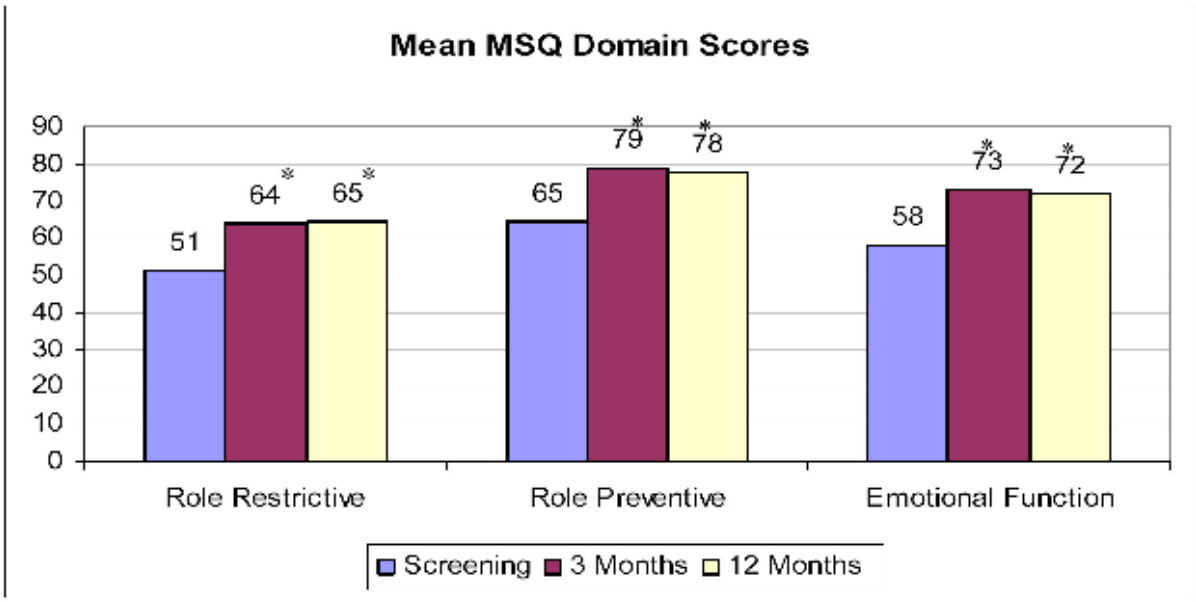
Migraine-Related Quality of Life Measure

HRQoL was evaluated in these studies using the Migraine-Specific Quality of Life Questionnaire (MSQ), Version 2.1 administered at screening, Month 3 and Month 12. The questionnaire consists of 14 items measuring how migraine affects HRQoL in 3 dimensions: Role Function—Restrictive (7 items), Role Function—Preventive (4 items), and Emotional Function (3 items). The domains were scored on a 0 (worst) to 100 (best) scale.

Migraine-specific Health-Related Quality of Life Results

The mean MSQ domain scores increased by 13 to 15 points following three months of treatment with *Treximet* ($P < 0.001$ vs. baseline), exceeding a clinically relevant improvement on each of the three domains.[23] In addition, these improvements were maintained through the 12 months of the study *(*$P <$ 0.001 vs. baseline). These results are shown in

Figure 4. The Effect of *Treximet* on Migraine-related Quality of Life Over 12 Months[10]



* Changes from baseline statistically significant ($P<0.001$) and clinical relevant as per minimally clinical important differences (MCID) thresholds (Role Restrictive = 6.80; Role Prevention = 8.72; Emotional Function = 5.76)

8.2 Impact of *Treximet* on Productivity

Productivity Measure

Lost productivity was evaluated in each of these studies using the instruments and methods described below. Results for these analyses demonstrated that lost productivity time was lower in migraine subjects treated with *Treximet* in all studies when compared to placebo. When lost workplace productivity and lost activity time were evaluated, subjects treated with *Treximet* also experienced significant reductions in both endpoints.

In studies evaluating the effect of *Treximet* on productivity, subjects completed the Productivity Assessment Questionnaire (PAQ) 24 hours after taking study drug.[15,16,19,20,90,91] The number of hours missed from work, hours worked with symptoms, and effectiveness at work during the 24 hours after taking study drug were recorded. Lost productivity was then calculated as:

- Lost Workplace Productivity = (hours missed from work) + ((hours worked with symptoms) * [(100 % work effectiveness)/100])

Lost work productivity was set to zero if the patient was not scheduled to work when the migraine attack occurred. Lost activity time was collected and calculated similarly:

- Lost Nonpaid Activities Time = (hours missed from nonwork activities) + ((100 % effectiveness at nonwork activities)/100) * (hours continued with nonwork activities with symptoms)

Total lost productivity (i.e., total disability time or total lost time) was the sum of lost work productivity and lost nonpaid activity time. Each of these productivity parameters were summarized by treatment group and compared statistically for *Treximet* versus other treatment groups using the Wilcoxon Rank-sum test adjusted for pooled investigator site

TREATMENT OF MODERATE TO SEVERE MIGRAINE PAIN

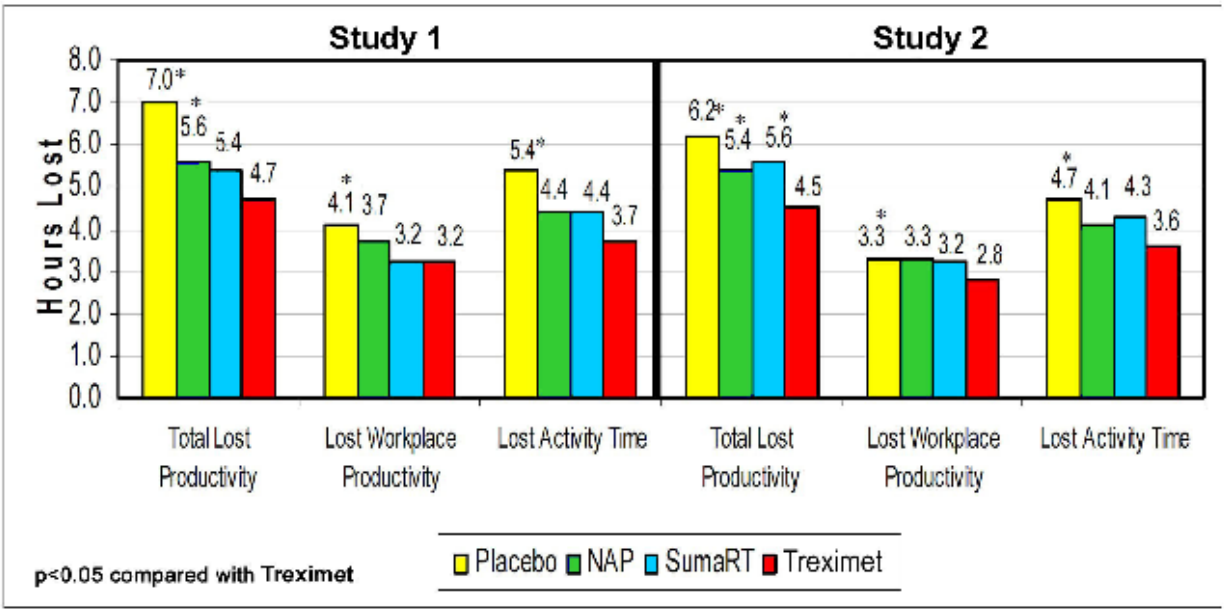
The efficacy and tolerability of *Treximet* were evaluated against sumatriptan (85 mg formulated with RT Technology™), naproxen sodium 500 mg, and placebo in two identical randomized, double-blind, parallel-group, single-attack studies.[24] A total of 2,911 subjects meeting International Headache Society (IHS) criteria for migraine with or without aura took study medication and had at least one post-baseline efficacy evaluation. The patient populations in both studies were predominantly Caucasian females with a mean age of 40 years (range 18-65). Subjects were instructed to treat a single migraine attack of moderate to severe pain severity, but were not permitted to take a second dose. Rescue medication was allowed beginning two hours post-dose; however, any ergot-containing compound, 5HT agonist, or NSAID-containing compound was excluded.

Productivity Results

Total lost productivity was significantly lower for subjects treated with *Treximet* in both studies.[15,16,90] In Study 301 (Study 1), total lost productivity was 33% lower in subjects treated with *STreximet* (4.7 hours) compared to subjects treated with placebo (7 hours; $P < 0.001$). Similarly, in Study 302 (Study 2), total lost productivity was 27% lower in subjects treated with *Treximet* (4.5 hours) compared to placebo (6.2 hours; $P < 0.001$). Overall, subjects treated with *Treximet* also experienced less impact on both workplace productivity and lost activity time.

Additionally, subjects treated with *Treximet* experienced 22% and 15% less impact on workplace productivity in Studies 301 and 302, respectively, compared to placebo ($P < 0.01$ for both studies). Finally, subjects treated with *Treximet* experienced 31% and 23% less impact on lost activity time in Studies 301 and 302, respectively, compared with the placebo group ($P < 0.01$ for both studies). Figure 5 details the results for all mean productivity loss during the 24 hours post-treatment for each of the treatment medications.

Figure 5. Productivity Loss during 24 hours Post-Treatment



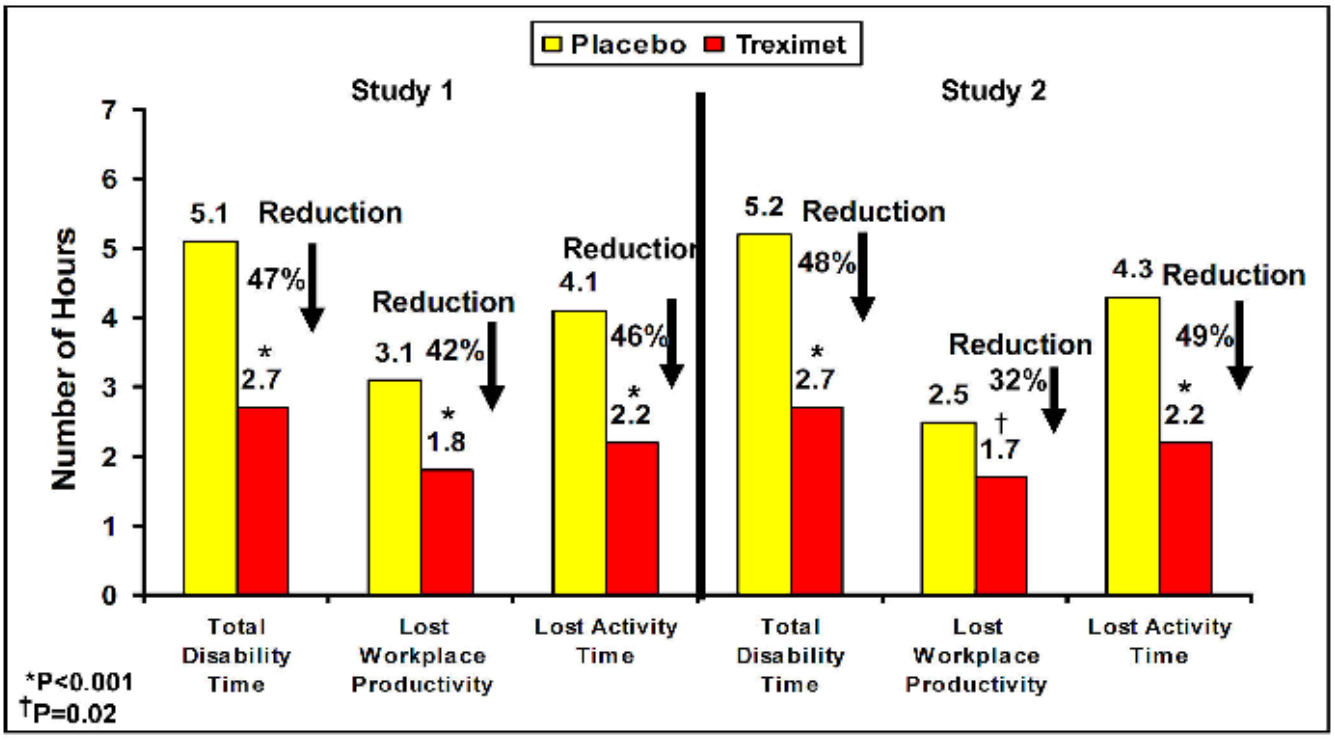
TREATMENT OF MILD MIGRAINE PAIN

The efficacy and tolerability of *Treximet* when treating mild migraine pain were evaluated in two identical randomized, double-blind, placebo-controlled, parallel group, single attack studies.[17,18] Subjects were eligible for study inclusion if they met IHS criteria for migraine with or without aura, aged 18 to 65 years old, and typically experienced an identifiable mild pain phase followed by moderate to severe migraine pain. A total of 1,305 subjects were randomized in a 1:1 ratio to receive *Treximet* or matching placebo. The patient populations in both studies were predominantly female (88%), Caucasian (86%), with a mean age of 41 years. Subjects were instructed to take one tablet of study medication during the mild pain phase and within one hour of pain onset; a second dose was not permitted. Rescue medication was permitted beginning two hours post-dose, but excluded any ergot-containing compound, 5HT agonist, or NSAID drug-containing compound.

Productivity Results

Total productivity time was significantly lower for subjects treated with *Treximet* [47% and 48% reductions in Study 998 (Study 1) and Study 999 (Study 2), respectively] compared to placebo ($P < 0.001$ for both studies). Subjects treated with *Treximet* also experienced statistically significant reductions in both workplace productivity and lost activity time. A 42% and 32% reduction in workplace productivity was observed in Studies 998 and 999, respectively ($P < 0.001$ for Study 998; $P = 0.02$ for Study 999). Subjects treated with *Treximet* experienced a 46% and 49% reduction in lost activity time in Studies 998 and 999 respectively, compared with the placebo ($P < 0.001$ for both studies). Figure 6 below outlines the mean productivity loss during the 24 hours post-treatment.

Figure 6. Mean Productivity Loss during 24 hours Post-Treatment[91]



CONSISTENCY OF RESPONSE OVER MULTIPLE MIGRAINE ATTACKS

Two identical randomized, double-blind, multicenter, placebo-controlled, 4-period crossover, multi-attack studies evaluated the consistency of response for *Treximet* when administered during the mild pain phase and within one hour of onset of headache pain for the acute treatment of migraine.[19,20] Subjects (n = 646 Study 632 and n = 620 Study 635) with IHS criteria defined migraine with or without aura were randomly assigned to one of five treatment sequences (see Table 23).

Table 23. Consistency of Response Studies: Five Treatment Sequences[19,20]

	Attack 1	Attack 2	Attack 3	Attack 4
Group 1	P	T	T	T
Group 2	T	P	T	T
Group 3	T	T	P	T
Group 4	T	T	T	P
Group 5	T	T	T	T
T = *Treximet*, P = matching placebo				

A total of 1135 subjects took at least one dose of study medication. The patient populations in both studies were predominately Caucasian females with a mean age of 41 years (range 18-66). Subjects were instructed to treat up to four eligible migraine attacks over a 4-month period. Rescue medication was allowed beginning two hours post-dose with the exception of ergot-containing compounds, barbiturates, opioids, or 5HT agonists. The recommended rescue medication was two naproxen sodium 220 mg tablets, then one additional tablet (220 mg) six hours later if needed, not to exceed three tablets in a 24 hour period.

Productivity Results

On average, subjects treated with *Treximet* missed significantly fewer total lost productivity hours in both studies compared to those taking placebo ($P < 0.05$). Additionally, subjects were more productive at both work and nonwork activities than subjects treated with placebo during most attacks. Results are presented in Table 24 below.

Table 24. Median Productivity Loss (Hours) during 24 Hours Post-Treatment[19,20]

	Study 103632			Study 103635		
Productivity Measure	***Treximet***	**Placebo**	***P* value**	***Treximet***	**Placebo**	***P* value**
Attack 1						
Lost productivity time	1.0	2.7	< 0.001	0.9	1.6	0.157
Lost activity time	1.2	2.5	< 0.001	1.0	1.9	0.007
Total lost time	1.8	3.3	< 0.001	1.5	2.6	0.002
Attack 2						
Lost productivity time	1.0	1.5	0.148	0.8	1.2	0.141
Lost activity time	1.0	1.4	0.091	0.6	2.1	< 0.001
Total lost time	1.6	2.1	0.046	1.2	2.8	< 0.001
Attack 3						
Lost productivity time	0.9	1.2	0.331	0.9	2.4	0.008
Lost activity time	1.0	1.6	0.025	0.6	1.9	0.008
Total lost time	1.5	2.5	0.017	1.4	2.1	0.036
Attack 4						
Lost productivity time	1.0	1.5	0.108	0.9	1.5	0.232
Lost activity time	1.0	2.0	< 0.001	0.6	2.3	< 0.001
Total lost time	1.5	2.5	0.003	1.2	2.6	< 0.001
Data represented as Lost Time Equivalents = hours missed + [(100 - % effectiveness) / 100 x hours with symptoms]						

TREATMENT OF MENSTRUAL MIGRAINE PAIN

The efficacy and tolerability of *Treximet* when treating menstrual migraine during the mild pain phase were evaluated in two identical randomized, double-blind, placebo-controlled, parallel-group, single-attack studies.[21,22] Adult women were eligible for study inclusion if they experienced headaches influenced by their menstrual cycle and met IHS criteria for migraine with or without aura. Eligible women were classified as meeting either pure menstrual migraine or menstrually-related migraine criteria. A total of 705 subjects were randomized to receive *Treximet* (n=354) or matching placebo (n=351). The female patient populations in both studies were predominantly Caucasian with a median age of 37-39 years (range 18 to 55). Subjects were instructed to treat their next menstrual migraine attack with a single tablet of *Treximet* or placebo during the mild pain phase, and within 1 hour of the onset of migraine pain. Rescue medication was allowed beginning at 2 hours post-dose, which included a second dose of *Treximet* but excluded any ergot-containing compound, 5HT agonist with the exception of *Treximet* or sumatriptan, analgesics containing morphine or codeine, a barbiturate or an opioid derivative, or an NSAID-containing compound with the exception of naproxen.

Productivity Results

Overall, subjects treated with *Treximet* missed fewer hours in work and nonwork activities than subjects treated with placebo.[21,22] Total lost productivity was also lower in subjects treated with *Treximet*. Results are shown in Table 25.

Table 25. Median Productivity Loss (LTE) During 24 Hours Post-Treatment[21,22]

	Study 105850			Study 105852		
Productivity Measure	***Treximet***	**Placebo**	***P* value**	***Treximet***	**Placebo**	***P* value**
Lost productivity time	0	0	0.889	0	0	0.336
Lost activity time	1.4	2.0	0.410	1.6	2.5	0.006
Total lost time	1.5	1.9	0.214	1.6	2.6	0.003
Data represented as Lost Time Equivalents = hours missed + [(100 - % effectiveness) / 100 x hours with symptoms]						

8.3 Patient Satisfaction with *Treximet*

Medication Satisfaction Measure

Medication Satisfaction was evaluated in the studies listed below using one of two different medication satisfaction questionnaires specifically developed to assess patient satisfaction with migraine therapy.

In the pivotal efficacy studies (MT400-301 and MT400-302) and the long-term safety study (MT400-303) satisfaction was measured at screening and 24 hours post treatment with the Patient Perception of Migraine Questionnaire (PPMQ), which assesses 8 attributes of migraine medications on a 7-point Likert scale ("very dissatisfied" to "very satisfied"). [15,16,17,18,19,20,21,22]Post-treatment satisfaction ratings were compared statistically with the Wilcoxon rank-sum test controlling for pooled investigator site as strata. In addition, the change in satisfaction scores from screening was calculated so that positive scores indicate improvement.

In the remainder of the studies, medication satisfaction was measured at 24 hours post dosing using the Revised Patient Perception of Migraine Questionnaire (PPMQ-R) which consists of 4 subscales: tolerability (10 items), efficacy (11 items), functionality (4 items), and ease of use (2 items) in addition to 3 ‘overall’ global satisfaction questions. Scores range from 0 to 100 with higher scores reflecting more satisfaction or higher tolerability. A 5-point score difference is considered clinically relevant (MID). The psychometric properties of the questionnaire have been evaluated and reported.[92]

TREATMENT OF MODERATE-SEVERE MIGRAINE PAIN

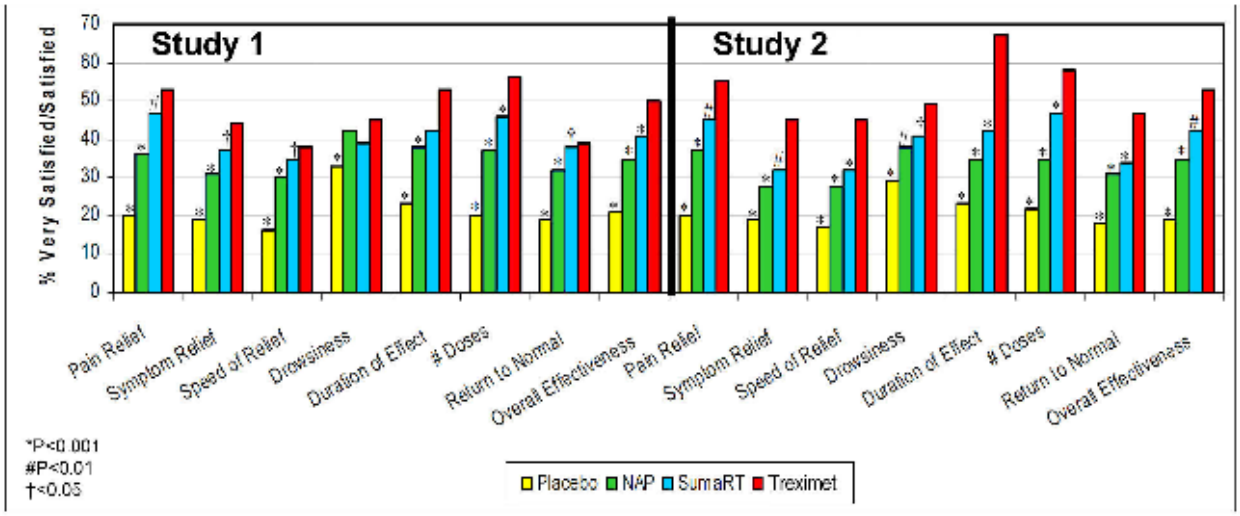
Medication satisfaction with *Treximet* were evaluated versus sumatriptan (85 mg formulated with RT Technology™), naproxen sodium 500 mg, and placebo in two identical randomized, double-blind, parallel group, single attack studies.[24] A total of 2,911 subjects with International Headache Society (IHS)

criteria defined migraine with or without aura took study medication and had at least one post-baseline efficacy evaluation. The patient populations in both studies were predominantly Caucasian females with a mean age of 40 years (range 18-65). Subjects were instructed to treat a single migraine attack of moderate to severe pain severity, but were not permitted to take a second dose. Rescue medication was allowed beginning two hours post-dose, however, any ergot-containing compound, 5HT agonist, or NSAID-containing compound was excluded.

Patient Satisfaction Results (PPMQ)

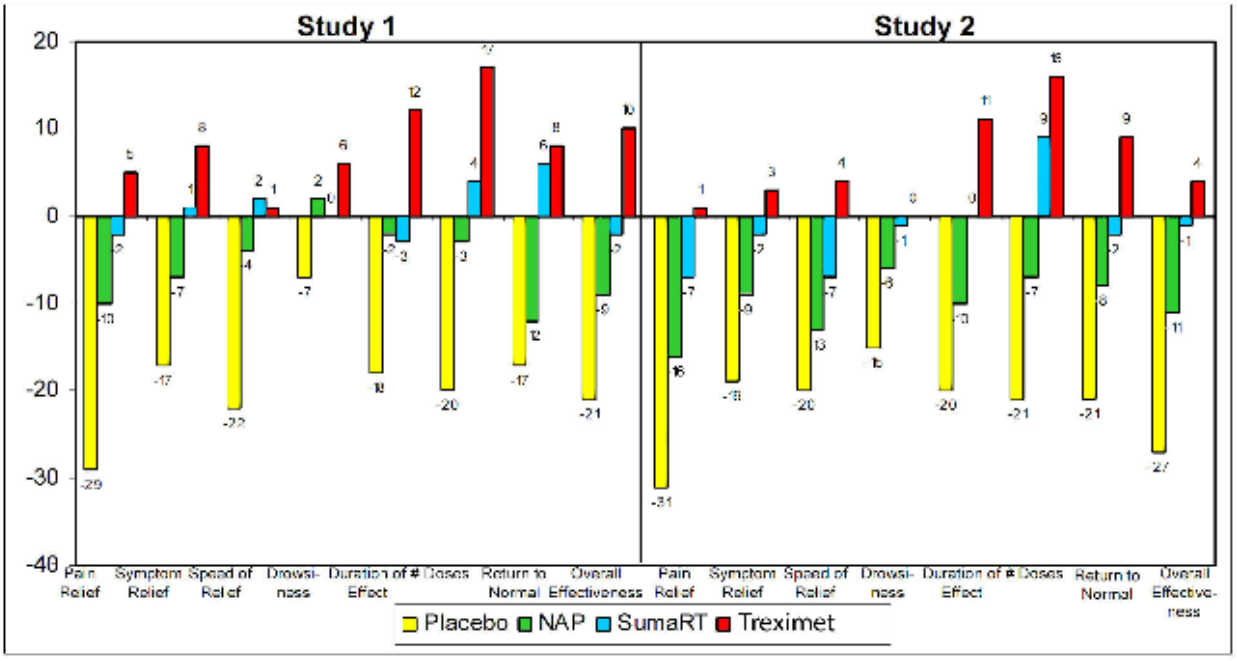
Subjects taking *Treximet* were significantly more satisfied with their treatment 24 hours post treatment than other groups in both studies (Figure 7).[15,16,90] In addition, subjects taking *Treximet* were significantly more likely to report being satisfied or very satisfied with their treatment on each of the 8 treatment attributes compared to all other treatments in both studies, with the exception of drowsiness in Study 1.

Figure 7. Percent of Subjects Satisfied/Very Satisfied with Treatment 24 hours Post Dosing



Satisfaction ratings were also compared with previous treatments reported by subjects during the screening visit (Figure 8).[15,16,90] Subjects taking *Treximet* reported higher rates of satisfaction compared to previous treatment for duration of effect (increase of 12% for Study 301 and 11% for Study 302), the number of doses needed for relief of symptoms (increase of 17% for Study 301 and 16% for Study 302), and the time it took to return to normal (increase of 8% for Study 301 and 9% for Study 302).

Figure 8. Absolute Change From Previous Treatment in the Percent of Subjects Satisfied/Very Satisfied With Study Treatment



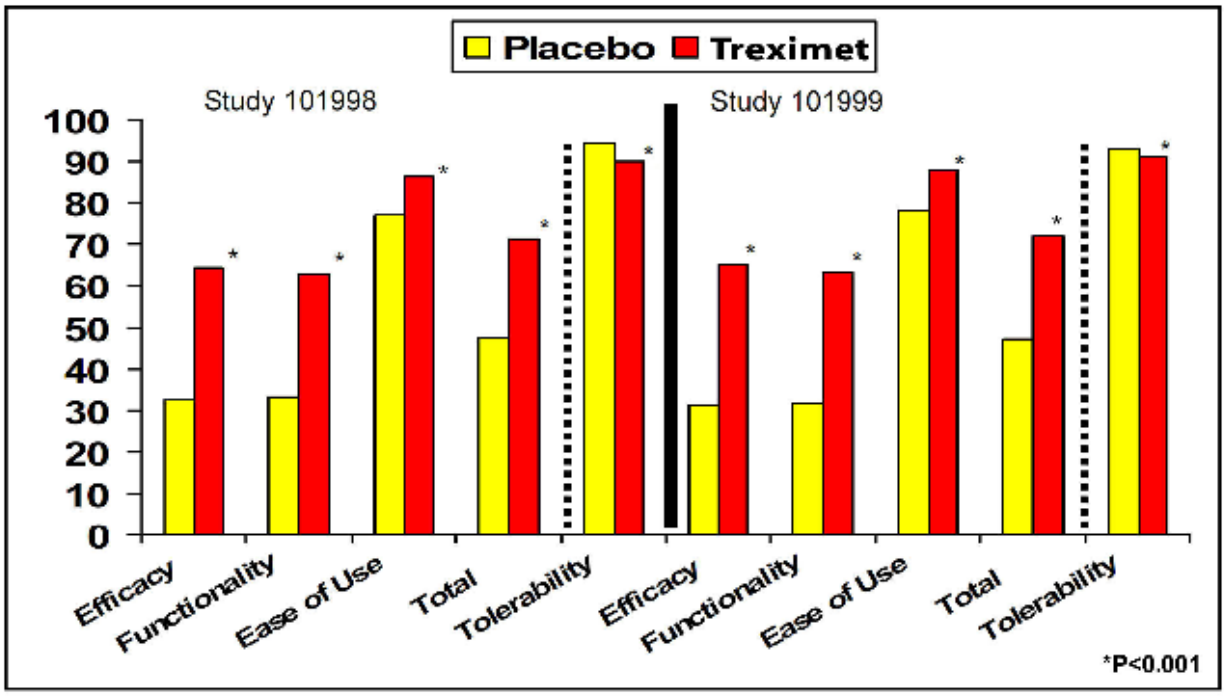
TREATMENT OF MILD MIGRAINE PAIN

Medication satisfaction with *Treximet* when treating mild migraine pain was evaluated in two identical randomized, double-blind, placebo-controlled, parallel group, single attack studies.[17,18] Subjects were eligible for study inclusion if they met the IHS criteria for migraine with or without aura (1.1 or 1.2), aged 18-65 years old, and typically experienced an identifiable mild pain phase followed by moderate to severe migraine pain. A total of 1,305 subjects were randomized in a 1:1 ratio to receive *Treximet* (n = 664) or matching placebo (n = 641). The patient populations in both studies were predominantly female (88%), Caucasian (86%), with a mean age of 41 years. Subjects were instructed to take one tablet of study medication during the mild pain phase and within one hour of pain onset; a second dose was not permitted. Rescue medication was permitted beginning two hours post-dose, except for any ergot-containing compound, 5HT agonist, or non-steroidal anti-inflammatory drug containing compound.

Patient Satisfaction Results

Subjects treated with *Treximet* were significantly more satisfied with their treatment 24 hours post-treatment compared to subjects treated with placebo in both studies as indicated by the Patient Perception of Migraine Questionnaire - Revised (PPMQ-R) total score as well as Efficacy, Ease of Use, and Functionality Subscales ($P < 0.001$; Figure 9).[91]

Figure 9. Mean PPMQ-R Scores at 24 hours post dosing[91]



Subjects treated with *Treximet* were also significantly more likely to report being satisfied or very satisfied on the PPMQ-R Global items related to efficacy and overall effectiveness in both studies ($P < 0.001$; Table 26).

Table 26. Percentage of Patients Satisfied or Very Satisfied on PPMQ-R Global Satisfaction Items[91]

		% of patients very satisfied / satisfied on PPMQ-R Global Satisfaction Items	
		Treximet	**Placebo**
Global Satisfaction Items		N = (280) (276)	N = (296) (259)
How effective medication is overall	Study 101998	57%*	21%
	Study 101999	61%*	19%
Side effects of medication	Study 101998	58%	52%
	Study 101999	64%†	53%
Overall satisfaction	Study 101998	55%*	23%
	Study 101999	60%*	20%
*$P < 0.001$ vs. placebo † $P = 0.008$ vs. placebo			

CONSISTENCY OF RESPONSE OVER MULTIPLE MIGRAINE ATTACKS

Medication satisfaction was reported in two identical randomized, double-blind, multi-center, placebo-controlled, 4-period crossover, multi-attack studies evaluating the consistency of response for *Treximet* when administered during the mild pain phase and within one hour of onset of headache pain for the acute treatment of migraine.[19,20] Subjects (n = 646 Study 1 and n = 620 Study 2) with IHS criteria defined migraine with or without aura were randomly assigned to one of five treatment sequences (see Table 27).

Table 27. Consistency of Response Studies: Five Treatment Sequences[19,20]

	Attack 1	Attack 2	Attack 3	Attack 4
Group 1	P	T	T	T
Group 2	T	P	T	T
Group 3	T	T	P	T
Group 4	T	T	T	P
Group 5	T	T	T	T
T = *Treximet*; P = matching placebo				

A total of 1135 subjects took at least 1 dose of study medication. The patient populations in both studies were predominately Caucasian females, with a mean age of 41 years (range 18-66). Subjects were instructed to treat up to four eligible migraine attacks over a 4-month period. Rescue medication was allowed beginning two hours post-dose with the exception of ergot-containing compounds, barbiturates, opioids, or 5HT agonists. The recommended rescue medication was two naproxen sodium 220 mg tablets, then one additional tablet (220 mg) six hours later if needed, not to exceed three tablets in a 24 hour period.

Patient Satisfaction Results

Subjects treated with *Treximet* were significantly more satisfied with their treatment 24 hours post-dose than placebo in both studies, as measured by the efficacy, functionality and total efficacy subscales ($P < 0.001$) in all attacks and provided significantly greater ease of use in attacks 1 and 2 for both studies and attack 4 ($P < 0.01$) for Study 1. [19,20] (See Table 28 and Table 29).

Table 28. Mean PPMQ-R Scores at 24 Hours Post-Dosing by Attack - Study 1[19]

	Attack 1		Attack 2		Attack 3		Attack 4	
	TRX n = 443	**Pbo** n = 123	**TRX** n = 421	**Pbo** n = 103	**TRX** n = 410	**Pbo** n = 99	**TRX** n = 394	**Pbo** n = 97
Efficacy	69*	41	70*	46	69*	51	73*	44
Function-ality	68*	41	69*	46	68*	52	70*	44
Ease of Use	89*	82	88*	83	88	86	89*	83
Total Efficacy	75*	55	76*	58	75*	63	77*	57
Tolerabil-ity	89	94†	91	92‡	91	92	91	93‡

TRX = *Treximet*; Pbo = placebo

* $P < 0.01$ vs. placebo

† $P < 0.001$ vs. *Treximet*

‡ $P < 0.05$ vs. *Treximet*

Table 29. Mean PPMQ-R Scores at 24 Hours Post-Dosing by Attack - Study 2[20]

	Attack 1		Attack 2		Attack 3		Attack 4	
	TRX n = 455	**Pbo n = 106**	**TRX n = 416**	**Pbo n = 110**	**TRX n = 400**	**Pbo n = 106**	**TRX n = 391**	**Pbo n = 94**
Efficacy	69*	42	72*	46	72*	42	74*	45
Tolerabil-ity	67*	44	70*	46	71*	42	72*	44
Ease of Use	88*	81	89*	82	88‡	85	88‡	83

TRX = *Treximet*; Pbo = placebo

* $P < 0.001$ vs. placebo

† $P < 0.001$ vs. *Treximet*

‡ $P < 0.05$ vs. placebo

	Attack 1		Attack 2		Attack 3		Attack 4	
	TRX n = 455	**Pbo n = 106**	**TRX n = 416**	**Pbo n = 110**	**TRX n = 400**	**Pbo n = 106**	**TRX n = 391**	**Pbo n = 94**
Total Efficacy	75*	56	77*	58	77*	56	78*	57
Tolerability	89	93†	90	93†	91	94†	92	93

TRX = *Treximet*; Pbo = placebo

* $P < 0.001$ vs. placebo

† $P < 0.001$ vs. *Treximet*

‡ $P < 0.05$ vs. placebo

Subjects treated with *Treximet* were also significantly more likely to report being satisfied or very satisfied on the PPMQ-R Global items related to overall satisfaction ($P < 0.001$) for all attacks in both studies [with the exception of attack 3 in study 1 ($P < 0.05$)] and efficacy ($P < 0.001$) for all attacks in both studies than subjects treated with placebo (See Table 30).

Table 30. Percentage of Patients Satisfied or Very Satisfied on PPMQ-R Global Satisfaction Items by Attack - Studies 1 and 2[19,20]

		% of patients satisfied/very satisfied on PPMQ-R Global Satisfaction Items							
		Attack 1		Attack 2		Attack 3		Attack 4	
		TRX	Pbo	**TRX**	Pbo	**TRX**	Pbo	**TRX**	Pbo
Global Satisfaction Items	Study 1	n = 443	n = 123	n = 421	n = 103	n = 410	n = 99	n = 394	n = 97
	Study 2	n = 455	n = 106	n = 416	n = 110	n = 400	n = 106	n = 391	n = 94
How effective is medication overall	Study 1	64%*	30%	64%*	37%	63%*	44%	68%*	36%
	Study 2	63%*	26%	68%*	41%	66%*	33%	66%*	32%
Side effects of medication	Study 1	59%	61%	65%	57%	66%	58%	68%†	56%
	Study 2	57%	61%	63%†	51%	64%	62%	69%†	57%
Overall satisfaction	Study 1	62%*	32%	64%*	39%	60%†	46%	66%*	39%
	Study 2	62%*	29%	67%*	40%	66%*	33%	70%*	33%

TRX = *Treximet*; Pbo = placebo

* $P < 0.001$ vs. placebo

† $P < 0.05$ vs. placebo

TREATMENT OF MENSTRUAL MIGRAINE PAIN

Medication satisfaction with *Treximet* when treating menstrual migraine at the mild pain phase was evaluated in two identical randomized, double-blind, placebo-controlled, Parallel-group, single-attack studies.[21,22] Adult women were eligible for study inclusion if they experienced headaches influenced by their menstrual cycle and met IHS criteria for migraine with or without aura. Eligible women were classified as meeting either pure menstrual migraine or menstrually-related migraine criteria. A total of 705 subjects were randomized to receive *Treximet* (n=354) or matching placebo (n=351). The female patient populations in both studies were predominantly Caucasian with a median age of 37-39 years (range 18 to 55). Subjects were instructed to treat their next menstrual migraine attack with a single tablet of *Treximet* or placebo during the mild pain phase, and within 1 hour of the onset of migraine pain. Rescue medication was allowed beginning at 2 hours post-dose, which included a second dose of *Treximet* but excluded any ergot-containing compound, 5HT agonist with the exception of *Treximet* or sumatriptan,

analgesics containing morphine or codeine, a barbiturate or an opioid derivative, or an NSAID-containing compound with the exception of naproxen.

Patient Satisfaction Results

Subjects treated with *Treximet* were significantly more satisfied with their treatment 24 hours post-dose compared to subjects treated with placebo in both studies as indicated by the PPMQ-R Total Score as well as Efficacy, Ease of Use, and Functionality Subscales ($P < 0.04$).[21,22] A significant difference was not observed between the treatment groups for the Tolerability (side effects) subscale in both studies. Subjects treated with *Treximet* were also significantly more satisfied on the PPMQ-R Global items related to effectiveness and overall medication satisfaction in both studies ($P < 0.005$) as compared with the placebo group. Results are shown in Table 31.

Table 31. Percentage of Patients Satisfied or Very Satisfied on PPMQ-R Global Satisfaction Items[21,22]

		% patients very satisfied / satisfied on PPMQ-R Global Satisfaction Items	
		Treximet	**Placebo**
Global Satisfaction Items		**n = 302 (297)**	**n = 319 (312)**
How effective medication is overall	Study 105850	59%*	41%
	Study 105852	68%†	30%
Side effects of medication	Study 105850	66%	61%
	Study 105852	60%	56%
Overall satisfaction	Study 105850	59%*	43%
	Study 105852	69%†	31%

* $P < 0.005$ vs. placebo

† $P < 0.001$ vs. placebo

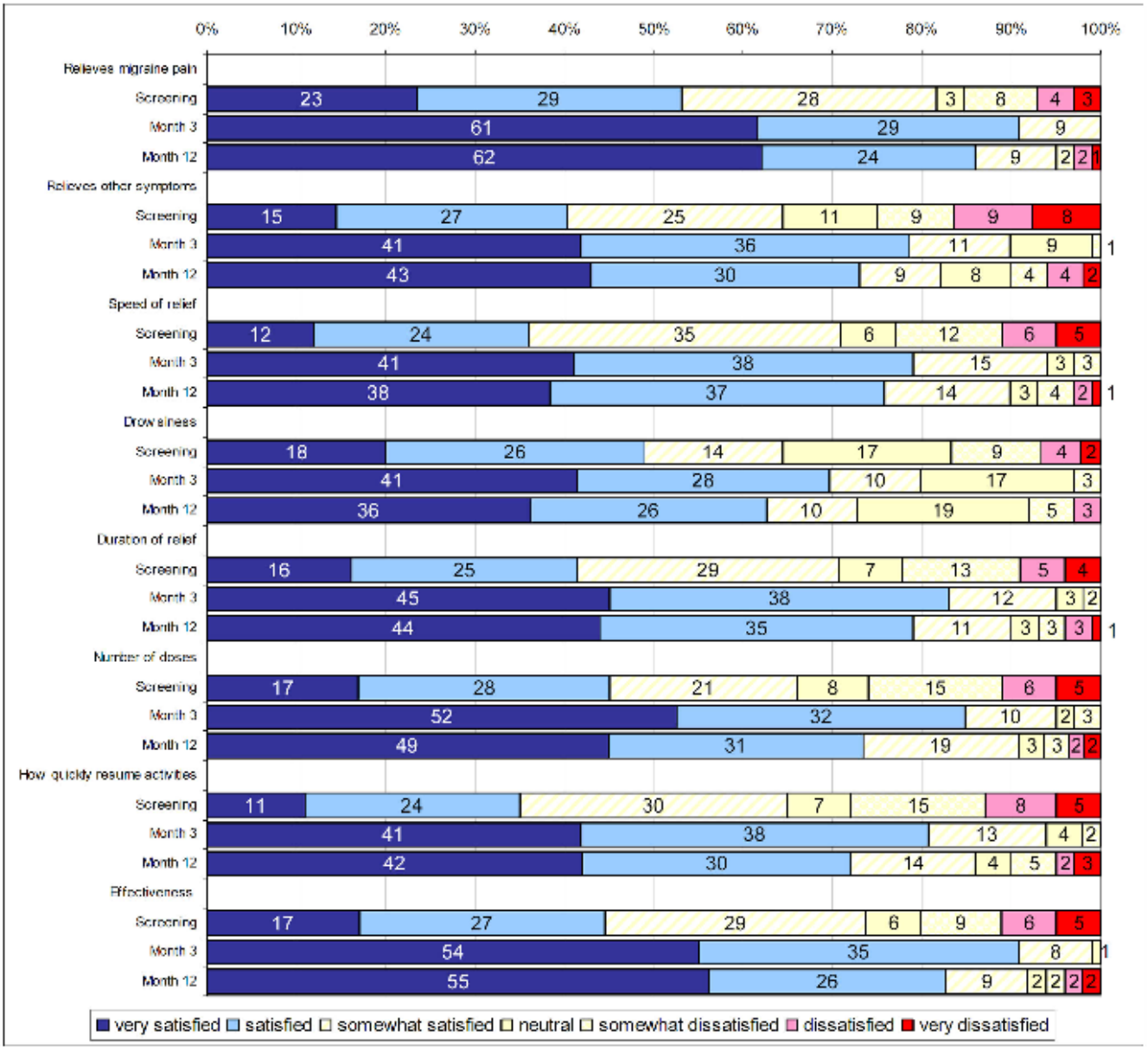
LONG-TERM SAFETY

An open-label, multi-center, multiple attack, repeat dose study examining the safety of single doses of *Treximet* in the acute treatment of migraine, with an optional second dose, was conducted over a 12 month period.[23] The study included adult outpatients, aged 1865, with a demonstrated history (≥6 months) of migraine with or without aura according to the IHS criteria and were instructed to take one tablet of *Treximet* for each migraine attack of moderate or severe intensity. A second dose of *Treximet* could be used to treat the same migraine attack if at least two hours had elapsed after taking the first dose and additional treatment was deemed necessary by the patient due to inadequate relief. Other rescue medications (excluding NSAIDs, ergots and other 5HT1 agonists) were allowed 2 hours after taking the last dose of study medication. The complete study population consisted of 565 subjects, with a total of 414 subjects completing six months (treating at least 12 attacks), and 362 Completed twelve months of the study (treating at least 24 attacks).

Patient Satisfaction

The PPMQ was administered to subjects at 3 time points in the 1-year study. At baseline to assess patient satisfaction with previous migraine therapy, at 3 months to assess their current migraine therapy, and at 12 months or early termination visit to assess patient satisfaction at the end of the study. The percentage of subjects satisfied/very satisfied increased on all 8 PPMQ items after 3 months ($P < 0.001$ vs. baseline) of therapy with *Treximet* and remained high through 12 months ($P < 0.001$ vs. baseline).[10] Individual PPMQ items are shown in Figure 10.

Figure 10. Satisfaction with *Treximet* Over 12 Months[10,86]



8.4 Impact of *Treximet* on Patient's Ability to Function:Clinical Disability

Ability to Function Measure

Functioning was evaluated in these studies using a single item questionnaire assessing a subject's self-rated ability to perform work or usual activities (functioning) at different time points during a migraine attack. In the two moderate to severe migraine pain studies (MT-400 301/302), functioning was measured from 0 (baseline) to 24 hours with a 4-point categorical scale (not impaired, mildly impaired, severely impaired, and required bed rest). [15,16]The number of subjects in the *Treximet* group who were functioning normally (ie, not impaired) was compared at 1 through 5 hours with the other treatment groups using a Cochran-Mantel-Haenszel test with pooled investigator site (small sites pooled) as the strata. In the remainder of the studies , functioning was only measured at 0 (baseline), two and four hours post-dose using a 5-point categorical scale (normal functioning, mildly impaired, moderately impaired, severely impaired, and required bed rest).[17,18,19,20,21,22] Analyses in these studies compared the percent of subjects who reported 'Normal' functioning at two and four hour time points.

Ability to Function (Clinical Disability) Measure

Ability to function, defined as the ability to perform work or usual activities, was measured hourly from 0 to 24 hours using a 4-point categorical scale [0 = not impaired (ability to function/work normally); 1 = mildly impaired; 2 = severely impaired; 3 = requiring bed rest].[15,16,90] Clinical disability category was defined as No Clinical Disability (score of none or mild), or Clinical Disability (score of severe or bed rest required), for each recorded time point.

Ability to Function Results

Prior to treatment, 50-60% in Study 1 and 40-50% of patients in Study 2 reported that their ability to function was severely impaired or that bed rest was required. At two and four hours post-dose, significantly more patients treated with *Treximet* reported no or mild impairment compared with the placebo group ($P < 0.001$) in each study (Table 32).

Table 32. Percentage of Patients with Normal Functioning or Mild Impairment at Two and Four Hours Post Dose [15,16,90]

	MT400-301			MT400-302		
Clinical Disability	***Treximet* (n = 361)**	**Placebo (n = 382)**	***P* Value**	***Treximet* (n = 364)**	**Placebo (n = 360)**	***P* value**
2 Hours	72	56	<0.001	77	64	<0.001
4 Hours	84	62	<0.001	84	68	<0.001
Sustained *	66	39	<0.001	70	48	<0.001
*Defined as continued responses of normal functioning from first report through 24 h post-dosing						

TREATMENT OF MILD MIGRAINE PAIN

Functioning was also evaluated in two identical randomized, double-blind, placebo-controlled, parallel group, single attack studies.[17,18] Subjects were eligible for study inclusion if they met the IHS criteria for migraine with or without aura (1.1 or 1.2), aged 18-65 years old, and typically experienced an identifiable mild pain phase followed by moderate to severe migraine pain. A total of 1,305 subjects were randomized in a 1:1 ratio to receive *Treximet* (n = 664) or matching placebo (n = 641). The patient populations in both studies were predominantly female (88%), Caucasian (86%), with a mean age of 41 years. Subjects were instructed to take one tablet of study medication during the mild pain phase and within one hour of pain onset; a second dose was not permitted. Rescue medication was permitted beginning two hours post-dose, except for any ergot-containing compound, 5HT agonist, or non-steroidal anti-inflammatory drug containing compound.

Functioning Results

At baseline, approximately 30% of subjects in both studies reported that their ability to function was moderately or severely impaired, or required bed rest. The majority of subjects in both studies reported that their ability to function was mildly impaired. At two and four hours post-dose, significantly more subjects treated with *Treximet* reported normal functioning compared with placebo ($P < 0.001$) in each study.

Table 33. Percentage of Patients with Normal Functioning at Two and Four Hours Post Dose [91]

	Study 101998			Study 101999		
Clinical Disability	***Treximet* (n=280)**	**Placebo (n=296)**	***P* value**	***Treximet* (n=280)**	**Placebo (n=296)**	***P* value**
2 Hours	47	23	<0.001	49	20	<0.001
4 Hours	73	36	<0.001	71	36	<0.001

Ability to Function (Clinical Disability) Measure

Ability to function, was measured at zero, two and four hours post-dose using a five-point categorical scale (normal functioning, mildly impaired, moderately impaired, severely impaired, and required bed rest).[19,20]

Ability to Function Results

A significantly greater percent of patients taking *Treximet* reported an ability to return to normal work or activities compared to those taking placebo at two and four hours post-dose and across all four attacks ($P < 0.05$). Results are presented in Table 34.

Table 34. Percentage of Patients with Normal Functioning at Two and Four Hours Post Dose[19,20]

	Study 103632					Study 103635				
Clinical Disability	***Treximet***		**Placebo**		***P* Value**	***Treximet***		**Placebo**		***P* Value**
	N	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Attack 1										
Baseline	437	12	123	14		452	16	104	20	
2 Hours		47		24	<0.001	453	49		27	<0.001
4 Hours		73		41	<0.001		72		42	<0.001
Attack 2										
Baseline	417	11	101	19		414	13	110	15	
2 Hours		47		32	0.004		51		29	<0.001
4 Hours	418	74		50	<0.001		73		42	<0.001
Attack 3										
Baseline	410	14	97	6		400	13	104	16	
2 Hours		48	98	35	0.019		46		26	<0.001
4 Hours		75		48	<0.001		73		42	<0.001
Attack 4										
Baseline	392	12	97	13		389	13	94	10	
2 Hours	393	49		28	<0.001	390	51		24	<0.001
4 Hours		74		42	<0.001		72		37	<0.001

TREATMENT OF MENSTRUAL MIGRAINE PAIN

Functioning when treating menstrual migraine at the mild pain phase was evaluated in two identical randomized, double-blind, placebo-controlled, parallel-group, single-attack studies.[21,22] Adult women were eligible for study inclusion if they experienced headaches influenced by their menstrual cycle and met IHS criteria for migraine with or without aura. Eligible women were classified as meeting either pure menstrual migraine or menstrually-related migraine criteria. A total of 705 subjects were randomized to receive *Treximet* (n=347) or matching placebo (n=358). The female subjects in both studies were predominantly Caucasian with a median age of 37-39 years (range 18 to 55). Subjects were instructed to treat their next menstrual migraine attack with a single tablet of *Treximet* or placebo during the mild pain phase, and within 1 hour of the onset of migraine pain. Rescue medication was allowed beginning at two hours post-dose, which included a second dose of Treximet but excluded any ergot-containing compound, 5HT agonist with the exception of *Treximet* or sumatriptan, analgesics containing morphine or codeine, a barbiturate or an opioid derivative, or an NSAID-containing compound with the exception of naproxen.

Functioning Results

At baseline, approximately 30% of subjects in both studies reported that their ability to function was moderately or severely impaired, or required bed rest.[21,22] Over half of the subjects in each study reported that their ability to function was mildly impaired. At two and four hours post-dose, significantly more subjects treated with *Treximet* reported normal functioning compared with the placebo group *(P* < 0.02) in both studies. Results are shown in Table 35.

Table 35. Percentage of Patients with Normal Functioning at Two and Four Hours Post-Dose [21,22]

	Study 105850			Study 105852		
Clinical Disability	***Treximet* (n=151)**	**Placebo (n=160)**	***P* Value**	***Treximet* (n=151)**	**Placebo (n=160)**	***P* Value**
2 Hours	39%	26%	0.010	44%	23%	<0.001
4 Hours	61%	48%	0.020	64%	43%	<0.001

Enclosure: Prescribing Information for *Treximet* Tablets

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Appendix

Table 10. *Treximet* Evidence Table: Efficacy and Safety Across Randomized Controlled Studies (ITT populations)

			Early Endpoints (% patients)								Sustained Endpoints (% patients)				Adverse Events	
Study Design/Study Number	**Patients (N)**	**Treat-ment Arms**	**PR 2 H**	**PR 4 H**	**PF 30 min**	**PF 1 H**	**PF 2 H**	**PF 4 H**	**MF 2 H**	**MF 4 H**	**2-24 H SPR**	**2-24 H SPF**	**Used Rescue**	**Recur-rence****	**Any AE**	**AEs (≥ 2% patients who took TRX)**
MS, R, DB, PG, SA studies. Patients randomized 1:1:1:1 to TRX, SUM 85 mg, NAP 500 mg, or PBO. Patients treated during moderate to severe pain. Rescue medication allowed at 2 H; second dose not permitted. MT400-301, MT400-302[24]	N=2,911	TRX n=364	57*†	72*†	1¶	5‡¶	30*†¶	50*†¶	23*	45*†	44*†	23*†	23*†¶	13	27	somnolence (4%) dizziness (3%) paresthesia (2%) nausea (4%) dyspepsia (3%) dry mouth (2%)
		SUM n=361	50	61	1	5	23	41	19	38	33	14	38	19	24	
		NAP n=356	43	54	1	2	16	26	14	24	28	10	39	22	13	
		PBO n=360	29	37	1	2	10	14	9	13	17	7	58	31	12	
		TRX n=362	65*†	78*†	0¶	4‡¶	34*†¶	56†*¶	29*	51*†	48*†	25*†	23*†¶	13	26	dizziness (5%) paresthesia (3%) somnolence (3%) nausea (3%) dry mouth (2%) chest discomfort (2%)
		SUM n=362	55	66	0	6	25	42	22	37	35	16	32	24	28	
		NAP n=364	44	55	0	3	15	27	13	25	30	10	38	16	14	
		PBO n=382	28	37	0	2	9	16	9	15	18	8	53	25	10	

TRX=*Treximet* tablet (85/500 mg); PBO=placebo; NAP=naproxen sodium 500 mg; SUM=sumatriptan 85 mg; MS=Moderate to Severe Paradigm; EI=Early Intervention Paradigm; H=Hours; PR=Pain Relief; PF=Pain-Free; MF=Migraine Free; SPR=Sustained Pain Relief; SPF=Sustained Pain-Free; R=Randomized; DB=Double-Blind; PC=Placebo-controlled; PG=Parallel-Group; SA=Single-Attack; MM=Menstrual Migraine; MRM=Menstrually-Related Migraine; OR=Odds Ratio; CI=95% confidence interval for odds ratio
*P<0.001 vs. placebo; †P<0.05 vs. sumatriptan 85 mg; ‡P<0.05 vs. placebo; § across attack comparisons made using repeated measures analysis; ‖ n (attacks)=1655 for 2 hour pain-free and n=1656 for sustained pain-free; ¶ post-hoc analysis; # unadjusted p value P<0.05 (comparison not adjusted for multiplicity); ** no statistics calculated, Recurrence = % patients who experienced the return of migraine pain within 24 hours post-dose / % patients who were pain-free at 2 hours

			Early Endpoints (% patients)								Sustained Endpoints (% patients)				Adverse Events	
Study Design/Study Number	**Patients (N)**	**Treat-ment Arms**	**PR 2 H**	**PR 4 H**	**PF 30 min**	**PF 1 H**	**PF 2 H**	**PF 4 H**	**MF 2 H**	**MF 4 H**	**2-24 H SPR**	**2-24 H SPF**	**Used Rescue**	**Recur-rence****	**Any AE**	**AEs (≥ 2% patients who took TRX)**
EI, R, DB, PC, PG, SA studies. Patients randomized 1:1 to TRX or PBO. Patients treated during mild pain and within 1 H of pain onset. Rescue medication allowed at 2 H; second dose not permitted. 101998[17], 101999[18]	N=1,111	TRX n=280	--	--	5‡	20*	52*	70*	45*	63*	--	45*	20*	13	11	nausea (3%)
		PBO n=296	--	--	2	7	17	25	15	24	--	12	47	30	7	
		TRX n=276	--	--	6‡	24*	51*	67*	46*	64*	--	40*	16*	22	14	dizziness (2%)
		PBO n=259	--	--	2	7	15	25	14	25	--	14	45	10	9	nausea (4%)
EI, R, DB, PC, 4-period, cross-over, multi-attack studies to assess consistency. Patients randomized to 1 of 5 treatment sequences. Patients treated during mild pain and within 1 H of pain onset. Patients treated up to 4 attacks over 4 months. Rescue medication allowed at 2 H; second dose not permitted. 103632§[19], 103635§[20]		TRX n=1665	--	--	3	24*	52*	75*	44*	69*	--	37*	--	--	9	no AEs to report
		PBO n=422	--	--	3	13	25	38	21	36	--	17	--	--	7	
		TRX n=165‖	--	--	4‡	25*	50*	72*	43*	66*	--	34*	--	--	13	dry mouth (3%)
		PBO n=416	--	--	2	9	20	33	17	31	--	12	--	--	9	nausea (3%) somnolence (2%) dizziness (2%)

TRX=*Treximet* tablet (85/500 mg); PBO=placebo; NAP=naproxen sodium 500 mg; SUM=sumatriptan 85 mg; MS=Moderate to Severe Paradigm; EI=Early Intervention Paradigm; H=Hours; PR=Pain Relief; PF=Pain-Free; MF=Migraine Free; SPR=Sustained Pain Relief; SPF=Sustained Pain-Free; R=Randomized; DB=Double-Blind; PC=Placebo-controlled; PG=Parallel-Group; SA=Single-Attack; MM=Menstrual Migraine; MRM=Menstrually-Related Migraine; OR=Odds Ratio; CI=95% confidence interval for odds ratio
*$P<0.001$ vs. placebo; †$P<0.05$ vs. sumatriptan 85 mg; ‡$P<0.05$ vs. placebo; § across attack comparisons made using repeated measures analysis; ‖ n (attacks)=1655 for 2 hour pain-free and n=1656 for sustained pain-free; ¶ post-hoc analysis; # unadjusted p value $P<0.05$ (comparison not adjusted for multiplicity); ** no statistics calculated, Recurrence = % patients who experienced the return of migraine pain within 24 hours post-dose / % patients who were pain-free at 2 hours

			Early Endpoints (% patients)								Sustained Endpoints (% patients)				Adverse Events	
Study Design/Study Number	**Patients (N)**	**Treat-ment Arms**	**PR 2 H**	**PR 4 H**	**PF 30 min**	**PF 1 H**	**PF 2 H**	**PF 4 H**	**MF 2 H**	**MF 4 H**	**2-24 H SPR**	**2-24 H SPF**	**Used Rescue**	**Recur-rence****	**Any AE**	**AEs (≥ 2% patients who took TRX)**
EI, R, DB, PC, PG, SA studies. Patients randomized 1:1 to TRX or PBO. Patients included with pure MM or MRM and dysmenorrhea at onset of menstruation. Patients treated during mild pain and within 1 H of pain onset. Rescue medication allowed at 2 H, including a second dose of TRX 105850[21], 105852[22]	N=621	TRX n=151	--	--	5	17	42*	60*	33#	55#	--	29‡	36‡	30	9	no AEs to report
		PBO n=160	--	--	3	11	23	36	19	29	--	18	53	19	9	
		TRX n=151	--	--	6	29*	52*	66*	44#	60#	--	38*	30*	27	23	nausea (4%) dry mouth (2%) dizziness (5%) paresthesia (2%)
		PBO n=159	--	--	3	8	22	30	19	27	--	10	67	49	11	

TRX=*Treximet* tablet (85/500 mg); PBO=placebo; NAP=naproxen sodium 500 mg; SUM=sumatriptan 85 mg; MS=Moderate to Severe Paradigm; EI=Early Intervention Paradigm; H=Hours; PR=Pain Relief; PF=Pain-Free; MF=Migraine Free; SPR=Sustained Pain Relief; SPF=Sustained Pain-Free; R=Randomized; DB=Double-Blind; PC=Placebo-controlled; PG=Parallel-Group; SA=Single-Attack; MM=Menstrual Migraine; MRM=Menstrually-Related Migraine; OR=Odds Ratio; CI=95% confidence interval for odds ratio
**P*<0.001 vs. placebo; †*P*<0.05 vs. sumatriptan 85 mg; ‡*P*<0.05 vs. placebo; § across attack comparisons made using repeated measures analysis; ‖ n (attacks)=1655 for 2 hour pain-free and n=1656 for sustained pain-free; ¶ post-hoc analysis; # unadjusted p value *P*<0.05 (comparison not adjusted for multiplicity); ** no statistics calculated, Recurrence = % patients who experienced the return of migraine pain within 24 hours post-dose / % patients who were pain-free at 2 hours

			Early Endpoints (% patients)								Sustained Endpoints (% patients)				Adverse Events	
Study Design/Study Number	**Patients (N)**	**Treat-ment Arms**	**PR 2 H**	**PR 4 H**	**PF 30 min**	**PF 1 H**	**PF 2 H**	**PF 4 H**	**MF 2 H**	**MF 4 H**	**2-24 H SPR**	**2-24 H SPF**	**Used Rescue**	**Recur-rence****	**Any AE**	**AEs (≥ 2% patients who took TRX)**
EI, R, DB, PC, cross-over, two-attack studies. Patients included if they reported having discontinued treatment with a short-acting triptan (rizatriptan, sumatriptan, almotriptan, zolmitriptan, and eletriptan) within a year due to non-response, poor response, or intolerance. Patients treated during mild pain and within 1 H of pain onset. Rescue medication allowed at 2 H; second dose not permitted. 106571[9], 106573[8]	N=376	TRX (n=136).[OR (CI)]	--	--	4% [2.91 (0.57, 14.95)]	19% [2.20 (1.05, 4.59)]‡	40% [3.19 (1.80, 5.65)]*	59% [4.93 (2.85, 8.54)]*	35% [3.18 (1.75, 5.76)]*	53% [3.88 (2.27, 6.61)]*	--	26% [4.50 (2.17, 9.36)]*	29% [0.24 (0.16, 0.38)]*	20%	11%	chest discomfort (2%)
		PBO (n=134), [OR (CI)]	--	--	2%	10%	17%	23%	14%	23%	--	8%	63%	52%	4%	
		TRX (n=134), [OR (CI)]	--	--	2% [1.00 (0.20, 5.07)]	25% [3.19 (1.60, 6.38)]‡	44% [4.69 (2.57, 8.55)]*	62% [8.11 (4.37 , 15.03)]*	35% [4.14 (2.20, 7.80)]*	57% [7.85 (4.17, 14.77)]*	--	31% [5.63 (2.76, 11.49)]*	22% [0.22 (0.14, 0.37)]*	22%	9%	
		PBO (n=133), [OR (CI)]	--	--	2%	9%	14%	17%	11%	15%	--	8%	55%	26%	5%	

TRX=*Treximet* tablet (85/500 mg); PBO=placebo; NAP=naproxen sodium 500 mg; SUM=sumatriptan 85 mg; MS=Moderate to Severe Paradigm; EI=Early Intervention Paradigm; H=Hours; PR=Pain Relief; PF=Pain-Free; MF=Migraine Free; SPR=Sustained Pain Relief; SPF=Sustained Pain-Free; R=Randomized; DB=Double-Blind; PC=Placebo-controlled; PG=Parallel-Group; SA=Single-Attack; MM=Menstrual Migraine; MRM=Menstrually-Related Migraine; OR=Odds Ratio; CI=95% confidence interval for odds ratio
*P<0.001 vs. placebo; †P<0.05 vs. sumatriptan 85 mg; ‡P<0.05 vs. placebo; § across attack comparisons made using repeated measures analysis; ‖ n (attacks)=1655 for 2 hour pain-free and n=1656 for sustained pain-free; ¶ post-hoc analysis; # unadjusted p value P<0.05 (comparison not adjusted for multiplicity); ** no statistics calculated, Recurrence = % patients who experienced the return of migraine pain within 24 hours post-dose / % patients who were pain-free at 2 hours